FORMULATION OPTIMIZATION AND IN–VITRO EVALUATION OF ORO-DISPERSIBLE TABLETS OF DEXIBUPROFEN

A dissertation submitted to

THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY

CHENNAI- 600 032.

In partial fulfillment of the requirements for the award of Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted

By

Reg No: 261311156

DEPARTMENT OF PHARMACEUTICS

EDAYATHANGUDY.G.S PILLAY COLLEGE OF PHARMACY

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SRINIVAS.NIMMATHOTA

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Under the guidance of

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CERTIFICATE

This is to certify that the dissertation entitled **"Formulation Optimization and In–Vitro Evaluation of Oro-Dispersible Tablets of Dexibuprofen"** submitted by **Srinivas. Nimmathota** (Reg No:261311156) in partial fulfillment for the award of degree of Master of Pharmacy to the Tamilnadu Dr. M.G.R Medical University, Chennai is an independent bonafide work of the candidate carried out under my guidance in the Department of Pharmaceutics, Edayathangudy. G.S.Pillay College of Pharmacy during the academic year 2013-2015.

Place: Nagapattinam **Prof. Dr.D.BabuAnanth, M.Pharm., Ph.D.,**

Date:

Prof.Dr.D.Babu Ananth,M.Pharm., Ph.D.,

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Place: Nagapattinam **Prof.Dr.D.BabuAnanth, M.Pharm., Ph.D.,**

Date:

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LIST OF ABBREVIATIONS

NDDS	Novel drug delivery system
DDS	Drug delivery system
ODT	Oro-dispersible tablets
MDT	Mouth dissolving tablets
NSAIA	Non steroidal anti-inflammatory agent
NSAID	Non steroidal anti-inflammatory drug
COX	Cyclo-oxygenase
UV	Ultra violet spectroscopy
FT-IR	Fourier transform infrared spectroscopy
HPLC	High performance liquid chromatography
MCC	Micro-crystalline cellulose
CCS	Croscarmellose sodium
SSG	Sodium starch glycollate
CP	Crospovidone
API	Active pharmaceutical ingredient
LT	Lyophilized tablet
USP	United states pharmacopoeia
BP	British pharmacopoeia
WHO	World health organization
ICH	International conference on harmonization
FDA	Food and drug authority
BCS	Biopharmaceutics classification system
RH	Relative humidity

1. INTRODUCTION

1.1 ORALLY DISINTEGRATING TABLETS [1, 2]

Among the different routes of administration, the oral route of administration continues to be the most preferred route due to various advantages including ease of ingestion, avoidance of pain, versatility and most importantly patient compliance. The important drawback of tablets and capsules dosage forms for pediatric and geriatric patients is they are facing difficulty in swallowing.

Nearly 35% of the general population, especially the elderly patients and children suffer from dysphasia or difficulty in swallowing, which results in high incidence of noncompliance and ineffective therapy. Swallowing problems also are very common in young individuals because of their poorly developed muscular and nervous systems. Other groups who may experience problems in swallowing conventional oral dosage forms are the patients with tremors of extremities, mentally ill, developmentally disabled, non co-operative patients and patients with reduced liquid intake plans or patients suffering from nausea. The swallowing problems are also common in some cases such as patients with motion sickness, sudden episodes of allergic attack or coughing and due to lack of water.

Recent advances in technology have presented viable dosage alternative for patients who may have difficulty in swallowing tablets or capsules. Traditional tablets and capsules administered with an 8-oz. glass of water may be inconvenient or impractical for some patients.

To overcome these problems, formulators have considerably dedicated their effort to develop novel drug delivery systems (NDDS) which enhance safety and efficacy of drug molecule and to achieve better patient compliance. One such approach is ‘Oral dispersible Tablets’, which disintegrate or dissolve in saliva and are swallowed without water as tablet disintegrate in mouth, this could enhance the clinical effect of

drug through pregastric absorption from the mouth, pharynx, esophagus. This leads to an increase in the bioavailability by avoiding first pass liver metabolism.

The centre for drug evaluation and research states an orally dissolving tablet to be "*A dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon tongue*." This system is recognized with other synonyms like fast dissolving tablets; melt in mouth tablets, porous tablets, rapidly disintegrating tablets, quick dissolving, and rapimelt tablets. Despite various nomenclatures the function and concept of all these Drug Delivery System (DDS) is similar.

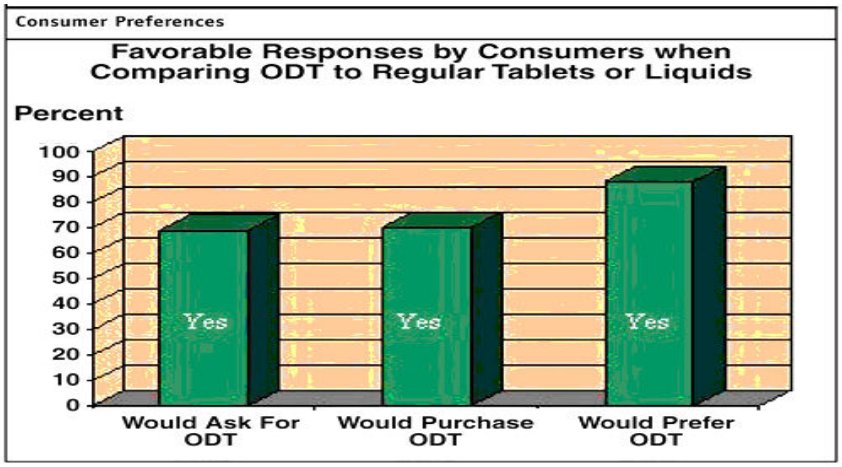


Figure 1 : Consumer Acceptance for ODT[3]

Above **figure 1**, shows that nearly 70% of the patient's population would ask for ODT and would purchase ODT. Whereas, nearly 90% of the patient's population would prefer only ODT compare to regular tablets or liquids.[3]

The advantages of orally disintegrating tablets are being recognized in both industry and academia. Their growing importance was underlined recently when the European Pharmacopoeia adopted the term **Oro-dispersible tablet** as a "tablet to be placed in the mouth where it disperses rapidly before swallowing".

Figure 2 : Disintegration of tablet in mouth[4]

Above **figure 2**, shows that as soon as ODT kept in the mouth it disintegrate rapidly within a matter of seconds and disperse thoroughly in oral cavity.[4]

Advantages of Oro-dispersible formulation[4]

- Improved patient compliance is the primary benefit of this technology.
- Administration to patients who cannot swallow and patients who refuse to swallow such as pediatric, geriatric and psychiatric patients.
- Can be produced at industrial scale more simply and more efficiently.
- No need of water for swallowing the dosage forms. This is highly convenient feature for the patients who are traveling or do not have immediate access to water.
- Superior taste of the tablet that helps to change the basic view of medications as the "bitter pill" particularly for pediatric patients.
- More rapid drug absorption through pre-gastric absorption from the mouth, pharynx and oesophagus.
- The fast dissolving dosage forms combines the benefit of liquid formulation with those of solid oral dosage forms.
- A wide range of drugs can be considered as a candidate for this dosage forms, (e.g. anti pyretic, analgesics, anti inflammatory agents, coronary vasodilators, antibiotics, anti-asthmatic agents, diuretics, anti arrhythmic, anti epileptics, antihistamines, anti- emetics and anti hypertensives).
- Added benefits of convenience and accurate dosing as compared to liquids.

Disadvantages of Oro-dispersible formulation [4]

- Drugs absorbed at specific site cannot be given in these dosage forms.
- These tablets show high friability, less hardness than conventional tablets.

1.2 CHALLENGES TO DEVELOP ORO-DISPERSIBLE TABLET [5]

1) Taste of the medicament:

As most of drugs are unpalatable, Orodispersible drug delivery system usually contain the medicament in a taste masked form. Delivery systems dissolve or disintegrate in the patient's mouth, thus releasing the active ingredients which come in contact with the taste buds and hence, taste masking of drug becomes critical for patient compliance.

2) Hygroscopicity:

Several Orodispersible dosage forms are hygroscopic and can't maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging.

3) Friability:

In order to allow Orodispersible tablets to dissolve or disintegrate in oral cavity, they are made of either porous or compressed into tablets with very low compression force, which makes the tablets friable which are difficult to handle, often requiring specialized peel-off blister packing.

Biopharmaceutical consideration:[6-7]

Elderly do not respond to the drug therapy in the same manner as young adult. Several age related changes in the gastrointestinal tract have the potential effect to alter the drug absorption, which effect overall drug absorption hence the drug efficacy.

Pharmacokinetics: The altered drug binding to serum albumin has been extensively studied in geriatric patients. A decrease in lean body and total body water is expected to result in decrease volume of distribution (Vd), of lipid soluble drugs. The decrease in liver volume and regional blood flow to the liver reduces the biotransformation of drugs through oxidation, reduction and hydrolysis. The drug excreted by renal clearance is slowed, thus half-life of renal excreted drugs increased.

Pharmacodynamics: Drug receptor interaction are impaired in elderly as well as in young ones due to the under development of organs.[8]

- Decreased ability of the body to respond baroreflexive stimuli, cardiac output, and orthostatic hypotension may seen in taking antihypertensive like prazocin.
- Decreased sensitivity of the CVS to β-adrenergic agonist and antagonist.
- Immunity is less and taken into consideration while administered antibiotics.
- Altered response to drug therapy- elderly show diminished bronchodilator effect of theophylline shows increased sensitivity to barbiturates.

- Concomitant illnesses are often present in elderly, which is also taken into consideration, while multi-drug therapy is prescribed.
- The incidence of diabetes and glucose tolerance is well documented and hence every attempt is made to avoid sugar-containing excipients.

Increasing the number of medication results in more complex dosing interval, dosage regimen and difficulties in dosage from design.

Conventional Techniques[4,5,9]

1) Tablet molding:

In this method, the delivery system is prepared in the form of tablets using water-soluble additives; allow the tablets to dissolve rapidly and completely in mouth. All the ingredients of the formulation are passed through fine mesh, dry blended, wetted with a hydro-alcoholic solvent and then compressed into tablets using low compression forces.

2) Freeze drying (Lyophilization):

Lyophilization is a pharmaceutical manufacturing technology, which allows drying of heat sensitive drugs and biological at low temperatures under conditions that allow removal of water by sublimation. Lyophilization results in preparations of highly porous, with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailability.

3) Spray drying:

Spray drying is a process by which highly porous fine powders can be produced. The composition contains a bulking agent (e.g. mannitol and lactose), disintegrant (e.g. sodium starch glycollate and croscarmellose sodium), an acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate) which when compressed into tablets shows fast disintegration and enhanced dissolution.

4) Sublimation:

Because of low porosity, compressed tablets composed of highly water-soluble excipients as tablet matrix material often do not dissolve rapidly in water. Porous tablets that exhibit good mechanical strength and dissolve quickly have been developed. Inert solid ingredients (e.g., urea, urethane, ammonium carbonate, camphor, naphthalene) were added to other tablet excipients and the blend was

compressed into tablet. Removal of volatile material by sublimation generated a porous structure. Compressed tablets containing mannitol and camphor have been prepared by sublimation technique. The tablets dissolve within 10-20 seconds and exhibit sufficient mechanical strength for particle use.

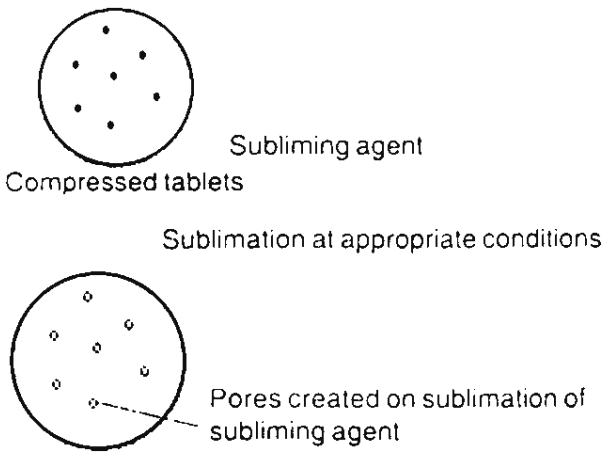


Figure 3 : Steps involved in development of the mouth dissolving tablets by sublimation technique

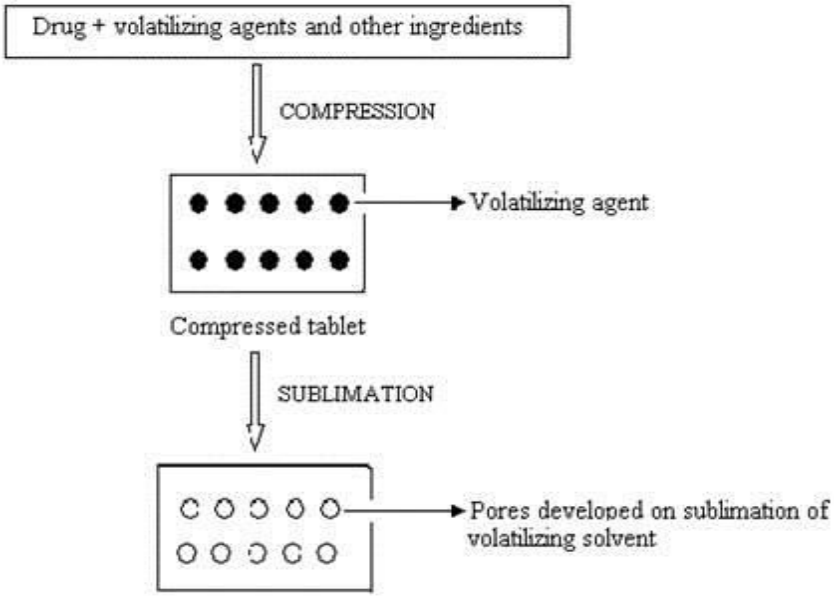


Figure 4 : Schematic Diagram of Sublimation Technique for preparation of MDT

5) Addition of Disintegrant:

Addition of disintegrant in fast dissolving tablets, leads to quick disintegration of tablets and hence improves dissolution. Microcrystalline cellulose, cross-linked carboxy methylcellulose, cross-linked polyvinyl pyrrolidones and partially substituted hydroxy propyl cellulose, absorb water and swell due to capillary action and are considered as effective disintegrant in the preparation of fast dissolving tablets.

6) Sugar-based excipient:

Sorbitol, Mannitol, dextrose, Xylitol, Fructose, Maltose, Isomalt, and Polydextrose have been used as bulking agents. Because of their high aqueous solubility and sweetness, which impart a pleasing mouth feel and good taste masking, nearly all formulations for rapidly dissolving tablets contain sugar-based materials.

7) Direct compression:[10]

Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Disintegrant efficiency is strongly affected by tablet size and hardness. Large and hard tablet have disintegration time more than that usually required. As a consequence, product with optional disintegration properties often have medium to small size and/or high friability and low hardness. Disintegrants have major role in disintegration and dissolution of mouth dissolving tablets made by direct compression. Disintegration efficiency is based on force equivalent concept, which is combined measurement of swelling force development and amount of water absorption. The simultaneous presence of disintegrant with high swelling force called disintegrating agent and substances with low swelling agent are claimed to be key factor for rapid disintergration of tablet; which also offer physical resistance.

8) Mass extrusion:[11]

The technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using menthol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to from tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby making their bitter taste.

1.3 PATENTED TECHNOLOGIES[5,9,12]

1) Zydis:-

This technology converts the mixture of active ingredient and water dispersible carrier materials into open matrix network that disintegrates rapidly using freeze-drying process. The network is highly porous solid foam, which allows rapid penetration of liquid and facilitates quick disintegration of the dosage unit. In Zydis technology, drug is added to a solution of carrier material (preferably gelatin) to obtain dispersion, and the dispersion is filled into preformed pockets of blister pack by automatic means, and freeze dried to produce the final dosage form.

2) Orasolv:-

This system essentially makes tablets that contain the taste masked active ingredients and an effervescent disintegrating agent, which on contact with saliva, rapidly disintegrates and released the active ingredient. The tablets are made by direct compression at very low compression forces in order to minimize oral dissolution time. The tablets produced are soft and friable.

Durasolv:-

The tablet made by this technology consists of drug, fillers and lubricant. Durasolv tablets are prepared by using conventional tableting equipment and have good rigidity. It is an appropriate technology for products requiring low amount of active ingredients.

3) Flash dose:-

Flash dose tablets consist of self-binding shear form matrix termed as “floss”. Shear form matrices are prepared by flash heat processing and are of two types. Single floss or Unifloss, consisting of a carrier, and two or more sugar alcohols, of which one is xylitol. Dual floss consists of a first shear form carrier material (termed “base floss”, contains a carrier and at least one sugar alcohol generally sorbitol), and a second shear form binder matrix (“binder floss”, contains a carrier and xylitol).

In flash heat process, the feed stock (carbohydrates including sugars and polysaccharides) is simultaneously subjected to centrifugal force and to a temperature gradient, resulting in discrete fibers. The preformed matrices obtained are partially crystallized and have good self-binding and flow properties. The so formed matrices are complex crystalline structures with high specific surface area and result in rapid dissolution rate of the drug. The shear form matrix is blended with drug and other

tableting ingredients, and compressed into tablets using conventional tableting equipment. Flash dose tablets are soft, friable and hygroscopic dosage forms, which require specialized packaging.

4) Wow tab:-

This process uses a combination of low mouldability saccharine (rapid dissolution) and high mouldability saccharine (good binding property) to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharine (e.g. lactose, mannitol) and granulated with a high mouldability saccharine (e.g. maltose, sorbitol) and compressed into tablets.

5) Flash tab:-

This technology involves the preparation of rapidly disintegrating tablet, which consists of an active ingredient in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques like coacervation, micro encapsulation, extrusion-spheronization or simple pan coating method. The micro crystals or micro granules of the active ingredient are added to the granulated mixture of excipient prepared by wet or dry granulation, and compressed into tablets.

6) Oraquick (kv pharmaceutical company inc.):[13]

The Oraquick mouth dissolving tablet formulation utilized a patent taste masking technology. KV pharmaceutical claims its microsphere technology, known as micromask, has superior mouth feel over taste masking alternatives. The taste masking process does not utilize solvents of any kind, and therefore leads to faster and more efficient production. Also lower heat of production than alternative fast dissolving technologies make oraquick appropriate for heat sensitive drugs. Oraquick claims quick dissolution in a matter of seconds, with good taste masking.

7) Shearform technology:[14-16]

The Shearform technology is based on preparation of floss that also known as shearform matrix, which is produced by subjecting a feedstock containing sugar carrier to flash heat processing. In this process, the sugar is simultaneously subjected to create an internal flow condition, which permits part of it to move with respect of the mass. The flowing mass exists through the spinning head that flings the floss, the floss so produced is amorphous in nature, which is further

chopped and re-crystallized by various techniques to provide uniform flow properties and thus facilitate blending.

The crystallized matrix is then blended with other tablet excipients and an active ingredient and other excipients can be blended with floss before carrying out re-crystallization. The shearform floss, when blended with the coated or uncoated microsphere, is compressed into tablets on slandered tabletting equipment.

8) Ceform technology:[17-19]

In Ceform technology microsphere containing active drug ingredient are prepared. The essence of Ceform microsphere manufacturing process involves placing a drug powder, containing substantially pure drug material or a special blend of drug material plus other pharmaceutical compounds and excipients into precision engineered, and rapidly spinning machine. The centrifugal force of the rotating head of Ceform machine throws the drug blend at high speed through small, heated openings. The carefully controlled temperature of the resultant microburst of heat liquefies the blend to form a sphere without adversely affecting the drug stability. The microsphere are then blended and/or compressed into the pre-selected oral delivery dosage form. The ability to simultaneously process both the drug and excipients generates a unique micro environment in which materials can be incorporated into the microsphere that can alter the characteristics of the drug substance, such as enhancing solubility and stability. The microsphere can be incorporated into a wide range of fast dissolving dosage forms such as EZ chew, spoon dose as well as conventional tablets.

1.4 TASTE MASKING[20,21]

Taste of a pharmaceutical product is an important parameter governing compliance. Bitter tasting drugs, drugs with an objectionable odour, or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation or entrapment prior to compression. Hence taste masking of oral pharmaceuticals has become important tool to improve patient compliance and the quality of treatment especially in pediatrics. Hence formulation of taste masked products is a challenge to the pharmacist.

As more than 50% of pharmaceutical products are administered orally, undesirable taste is one of the important formulation problems that can be encountered with

certain drugs. Oral administration of bitter drugs with acceptable level of palatability is a key issue for health care providers especially with pediatrics and geriatric patient. Thus, elimination or reduction of bitterness is an important issue during design of oral pharmaceutical formulations.

A major component of success in orally disintegrating tablets (ODT) is good taste. If the product taste good, ODT formulations are emerging and gaining popularity in the industry and have a significant impact on patients of all ages. ODT tablets dissolve or disintegrate in the oral cavity in a relatively short time and do not need to be swallowed with water. This has made taking medication easier, especially for children and the elderly who have traditionally had difficulties in swallowing more conventional dosage forms. The single most significant issue with ODT is the bitterness of the drug that can be exposed, and combining this with the right flavors/sweetness levels will result in a superior product.

Four fundamental sensations of taste have been described :

- Sweet and salty, at tip.
- Sour, at sides.
- Bitter, at back.

1.5 METHODS OF TASTE MASKING [21]

Various techniques available for masking bitter taste of drugs include:

1.5.1 Taste masking with ingredients such as flavors, sweeteners and amino acids.

1.5.2 Taste masking by polymer coating.

1.5.3 Inclusion Complexes with β-Cyclodextrin Derivative.

1.5.4 Taste masking by ion-exchange resins.

1.5.5 Miscellaneous taste masking technologies.

1.5.1 Taste masking with ingredients such as flavors, sweeteners and amino acids. [21]

Addition of flavors and sweeteners is the simplest approach for taste masking especially in pediatric formulations. Besides taste masking, flavors can also improve aesthetic appeal of the products. However this approach is not very successful for highly bitter and highly water soluble drugs.

Discover the flavoring agent best suited to mask an unpleasant taste is often a very empirical matter. Experience and experimentation have produced some general guidelines regarding the type of flavor best suited to mask a given taste. Such recommendations are listed in **Table 1**.

Table 1 : List of flavors[21]

Taste	Masking flavor
Salty	Cinnamon, Raspberry, Orange, Apple, Butterscotch, Glycyrrhiza (Licorice) syrup.
Sweet	Fruit berry, Vanilla, Acacia syrup
Bitter	Cocoa, Chocolate- Mint, Wild Cherry, Walnut Glycyrrhiza (licorice), Eriodictyon, Raspberry syrup.
Sour	Fruit citrus, cherry syrup

Sweeteners: Aspartame is a prominent sweetener for bitterness reduction. A concentration of as small as 0.8% was effective in reducing the bitterness of a 25% formulation of acetaminophen.

Artificial sweeteners like neohesperidine dihydrochalone which is a bitterness suppressor and flavor modifier, elicits a very intense sweet taste. Vitamins containing oral solutions are rendered bitterness free by adding sugars, amino acids, and apple flavors.

1.5.2. Taste masking by polymer coating[21]

Coating is an extremely useful technique for a number of applications, but its major application is in masking the unpleasant taste. Various inert coating agents can be used to coat bitter drugs. They include starches; polyvinyl pyrrolidones (povidone) of various molecular weights, gelatin, methylcellulose, hydroxymethylcellulose, microcrystalline cellulose and ethyl cellulose. These coating agents simply provide a physical barrier over the drug particles. One of the most efficient methods of drug particle coating is the fluidized bed coating. In this approach, powders as fine as 50 mm are fluidized in an expansion chamber by means of heated, high-velocity air, and the drug particles are coated with a coating solution introduced

usually from the top as a spray through a nozzle. Increasing the length of the coating cycle can increase coating thickness.

1.5.3. Inclusion Complexes with β-Cyclodextrin Derivative[22]

In inclusion complex formation, the drug molecule fits into the cavity of a complexing agent, i.e., the host molecule, forming a stable complex. The complexing agent is capable of masking the bitter taste of drug by either decreasing its oral solubility on ingestion or decreasing the amount of drug particles exposed directly to taste buds, thereby reducing the perception of bitter taste. This method is most suitable only for low dose drugs. Vander-vales forces are mainly involved in inclusion complexes. β - Cyclodextrin is the most widely used complexing agent for inclusion type complexes. It is a sweet, nontoxic, cyclic oligosaccharide obtained from starch.

The strong bitter taste of carbetapentane citrate was reduced to approximately 50% by preparing a 1:1 complex with β-Cyclodextrin. Palatable ibuprofen solutions are prepared by forming inclusion complexes with Hydroxy Propyl β-Cyclodextrin respectively. The complex masked the bitter component but created a sore taste that was masked by sweeteners.

1.5.4. Taste Masking by Ion-Exchange Resins[23]

Ion exchange resins are solid and suitably insolubilized high molecular weight polyelectrolyte's that can exchange their mobile ions of equal charge with the surrounding medium reversibly and stochiometrically. They are available in desired size ranges. Bitter cationic drugs can get adsorbed on to the weak cation exchange resins of carboxylic acid functionally to form the complex which is not bitter. Further resinates can be formulated as lozenges, chewing gum, suspension or dispersible tablet and mask the taste. Drugs are attached to the oppositely charged resin substrates or resinates through weak ionic bonding so that dissociation of the drug-resin complex does not occur under salivary pH conditions. This suitably masks the unpleasant taste and odors of drugs.

Ion exchange resins can be classified into four major groups.[23]

1. Strong acid cation exchange resin: Eg - Amberlite IRP-69, Indion-224.
2. Weak acid cation exchange resin: Eg. - Amberlite IRP-65, Indion-234S,

   Indion-204
3. Strong base anion exchange resin: Eg. - Amberlite IRP-276.

4. Weak base anion exchange resin: Eg. - Dimethylamine resin

1.6 ROLE OF DISINTEGRANT:[24]

For tablets, it is necessary to overcome the cohesive strength introduced into the mass by compression. Therefore, it is usual practice to incorporate excipients called disintegrant, which will include during formulation. Tablets containing a disintegrant break up rapidly in the water because of the sudden and immediate application of the stress. However, when a tablet containing such disintegrant is exposed to water stress is built up slowly and tablet absorbs some of the strain. For most tablets the most important step is the breakdown of the tablet into the smaller particles or granules, this step is known as disintegration.

Superdisintegrant are the agents added to tablet and some encapsulated formulations to promote the breakup of the tablet and capsule "slugs' into smaller fragments in an aqueous environment there by increasing the available surface area and promoting a more rapid release of the drug substance. They promote moisture penetration and dispersion of the tablet matrix. Tablet disintegration has received considerable attention as an essential step in obtaining fast drug release.

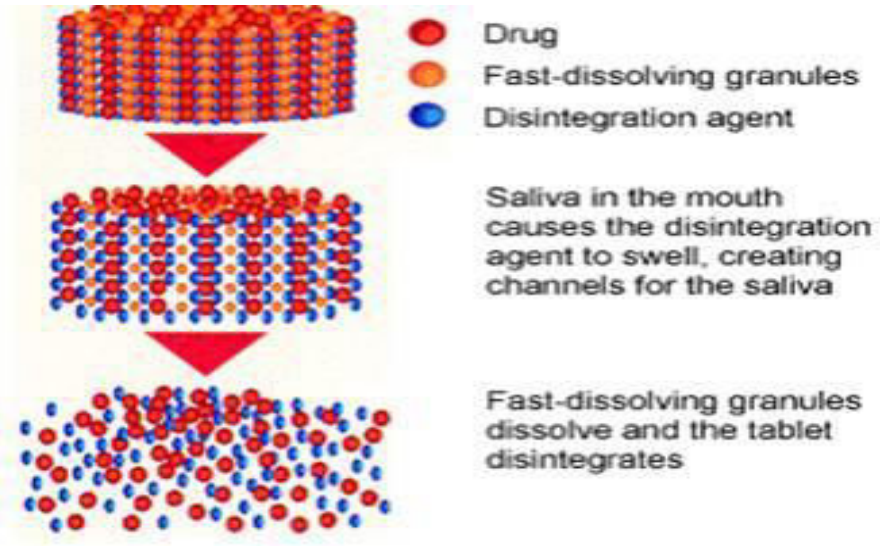


Figure 5 : Mechanism of Action of Superdisintegrants

Mechanism action of disintegrants

- By capillary action
- By swelling
- Due to deformation
- Due to disintegrating particle/particle repulsive forces
- Because of heat of wetting
- Due to release of gases
- By enzymatic action

Capillary action: Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipient and on tabletting conditions. For these types of disintegrants, maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles[25].

Swelling: Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down[25].

Due to deformation: Hess had proved that during tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure

when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during

compression[13,25].

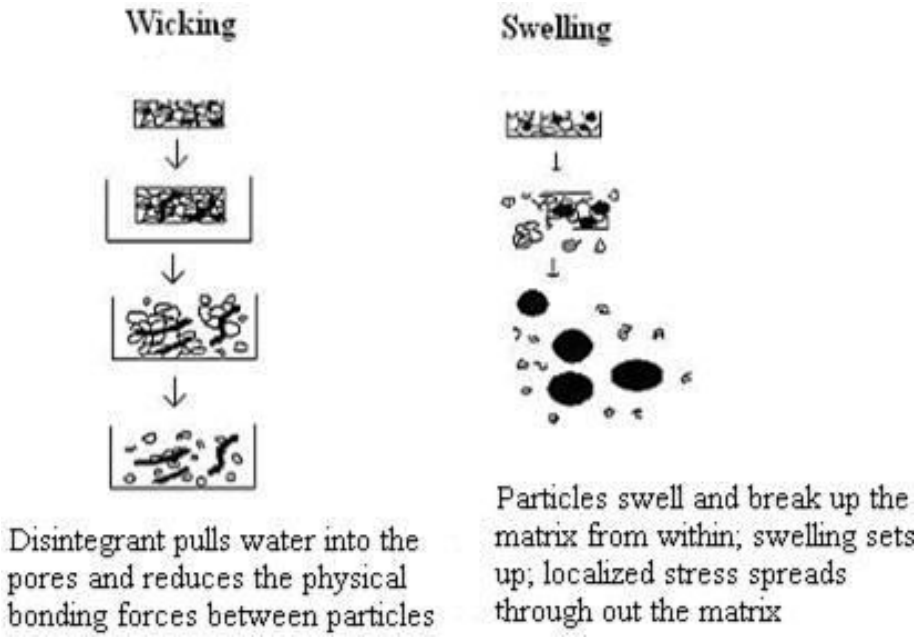


Figure 6 : Disintegration of Tablet by Wicking and Swelling

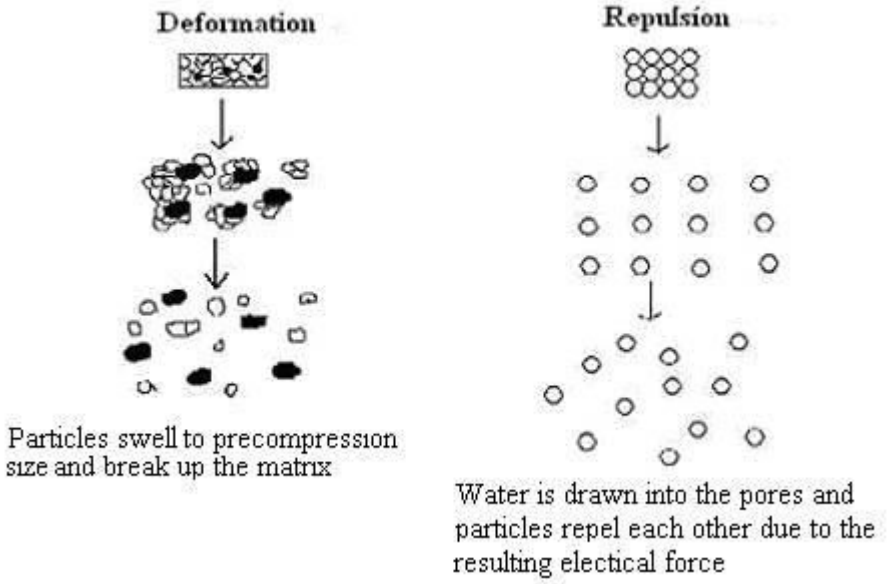


Figure 7: Disintegration by Deformation and Repulsion

Disintegration of tablet by repulsion: Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrants.

Guyot- Hermann has proposed a particle repulsion theory based on the observation that no swelling particle also causes disintegration of tablets. The electric repulsive forces between

particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking[13,25].

Heat wetting: When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of

tablet. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents[25].

Due to release of gases: Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid.

The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation[25].

By enzymatic action: Here, enzymes present in the body act as disintegrants. These enzymes destroy the binding action of binder and helps in disintegration. Actually due to swelling, pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration[25].

Methods of Incorporating Disintegrants into Tablets[26,27,28]:

There are two methods of incorporating disintegrating agents into the tablet as described below

- **Internal Addition (Intragranular):** In Internal addition method, the disintegrant is mixed with other powders before wetting the powder mixtures with the granulating fluid. Thus the disintegrant is incorporated within the granules.
- **External Addition (Extragranular) :** In external addition method, the disintegrant is added to the sized granulation with mixing prior to compression.
- **Partly Internal and External:** In this method, part of disintegrant can be added internally and part externally. This results in immediate disruption of the tablet into previously compressed granules while the disintegrating agent within the granules produces additional erosion of the granules to the original powder particles.

2.AIM AND OBJECTIVES

Dexibuprofen is an non-steroidal anti-inflammatory drug (NSAID) , a propionic acid derivative with analgesic and antipyretic properties. Dexibuprofen, (S(+)-ibuprofen) is a pharmacologically active form and is more potent than Ibuprofen, which contains equal quantities of R(−)- and S(+)-enantiomers. It is a bitter drug. Dexibuprofen inhibits cyclooxygenases and activates peroxisome proliferators-activated receptors; both of these actions result in reduced inflammation.

The aim of present work was to design and evaluate orally disintegrating tablets (ODTs) containing Dexibuprofen using superdisintegrants and wherein its bitter taste is also masked.

OBJECTIVES OF THE RESEARCH WORK

Broadly, the work would endeavour to achieve the following objectives:

1. Selection of a model non-steroidal anti-inflammatory drug (NSAID), (Dexibuprofen) based on pharmacokinetic parameters suitable for formulating into an ODT.
2. Selection of appropriate excipients including superdisintegrants (crosscarmellose sodium, crospovidone, sodium starch glycollate) to develop the dosage form based on physico-chemical properties and compatibility of the Active Pharmaceutical Ingredient (API) and excipients.
3. Preparation of standard calibration curve for Dexibuprofen.
4. Formulation development of fast disintegrating tablet by direct compression method.
5. Characterization and evaluation of the formulations

   I. Pre-compression parameter:

      a. Drug excipient compatibility studies: Comparison of drug and its combination with various polymers with FTIR.

      b. Evaluation of powder: Bulk density, Tapped density, Angle of repose, compressibility index.

   II. Post compression parameters:

      a. Appearance and its dimension measurements

b. Weight variation test

c. Wetting time

d. Water absorption ratio

e. Hardness test

f. Friability test

6. *In vitro* evaluation of formulation
   a. *In vitro* disintegration studies

   b. *In vitro* dissolution studies and curve fitting analysis

7. Optimization of the dosage form based on evaluated parameters to meet official &/or pharmacokinetic specifications.
8. Stability Study of the formulation as per ICH guidelines.

PLAN OF WORK

1. Literature review
2. Selection of drug and excipient
3. Preformulation study.
   - Organoleptic characteristics
   - Solubility of drug
   - Particle size distribution.
   - Physico-mechanical characterization.
   - Moisture content.
   - Drug potency Calculaion.
   - Drug-excipient Compatibility study.
4. Formulation of tablets by Direct Compression technique using Superdisintegrants.
5. Evaluation of the formulated tablets.
   - Thickness
   - Hardness and friability
   - Disintegration time
   - Weight variation
   - Wetting time
   - Water absorption ratio
   - *In vitro* Dissolution
6. Optimization of Selected formula.
7. Stability study of optimized formulation.
8. Result and discussion.

3. REVIEW OF LITERATURE

Fukami *et al.,* [29] was prepared rapidly disintegrating tablets using glycine as a disintegrant. They evaluated the disintegration behavior of tablets in oral cavity containing carboxymethyl cellulose showed the least wetting time 3 seconds with 4 kg hardness and showed the fastest disintegration due to excellent wetting property. They also studied the effect of ethanzamide and ascorbic acid on disintegration time. Result shows that ethanzamide has no effect on disintegration property. However, the disintegration time increases with ascorbic acid.

Moen and Keating [30] had developed a new fast-disintegrating Sumatriptan tablet with the goal of speeding absorption and onset of effect compared with standard Sumatriptan tablets. Compared with placebo, pain relief was significantly greater with Sumatriptan fast disintegrating tablets 100mg at 25 and 17 minutes following administration and with Sumatriptan fast disintegrating tablets 50mg at 50 and 30 minutes following administration, to severe migraine.

Mizumoto *et al.,* [31] was prepared novel fast disintegrating tablets using commonly used sugar as low and high compressible categories. They improved the compressibility of low compressible saccharides by coating the granules with high compressible saccharides to enable fast disintegration and changed the crystal habit by the process and achieved sufficient hardness.

Shirwaikar and Ramesh [32] had formulated Atenolol using super disintegrant such as sodium starch glycollate, croscarmellose sodium (Ac-Di-sol) and crospovidone. Dry granulation method was used to prepare tablets. Various physical parameters considered are water uptake studies, *In vitro* release and stability profile. Ac-Di-sol proved to be best of the three super disintegrant and showed the highest water uptakes. There was no change after stability study of the tablets.

Udupa *et al.,* [33] was reported the preformulation, preparation and evaluation of Nimesulide dispersible tablets by direct compression method. The tablets were prepared using microcrystalline cellulose as directly compressible vehicle, starch and sodium starch glycollate combination as super disintegrant. The formulations were evaluated for hardness, weight variation, uniformity of dispersion, drug content disintegration time, dissolution rate and stability studies. The optimized formula showed less disintegration time and more dissolution than marketed product.

Mishra *et al.,* [34] had developed Ora-Solv technology. In this system active medicament is taste masked by using effervescent disintegrating agent. Tablets was made by direct compression technique at low compression force in order to minimize oral dissolution time.

Baldi and Malfertheiner [35] was prepared Lansoprazole fast disintegrating tablet a new, patient-friendly and more convenient formulation of Lansoprazole, which can be taken with or without water. It represents an innovative drug delivery system, comprising enteric-coated micro granules of Lansoprazole compressed with an inactive, rapidly dispersing matrix to form a tablet. Alternatively, the tablet can be swallowed with a drink of water. Studies have shown that the bioavailability of Lansoprazole fast disintegrating tablet is comparable to Lansoprazole capsules, at both 15 and 30 mg doses.

Ahmed *et al.,* [36] had developed Ketoprofen tablets which dissolve rapidly in the mouth, therefore needing not to be swallowed. The solubility and dissolution rate of poorly water-soluble Ketoprofen was improved by preparing lyophilized tablets (LT) of Ketoprofen using freeze-drying technique. Results obtained from dissolution studies showed that lyophilized tablets of Ketoprofen significantly improved the dissolution rate of the drug compared with the physical mixture and the plain drug.

Seager [37] was studied Zydis formulation which is a unique freeze dried tablet in which drug was physically entrapped or dissolved within the matrix of fast dissolving carrier material. When a zydis unit was put into the mouth, the freeze dried structure disintegrates instantaneously and does not require water to for swallowing.

Ohkuma *et al.,*[38] was prepared and evaluated a fast disintegrating tablet containing Nicordial loaded particles with 1-4% croscarmellose sodium in addition to D-mannitol and lactose was prepared and examined. The results suggested that formulation had masking effect against the bitter taste and irritation of the drug.

Shenoy *et al.,*[39] had developed fast dissolving tablets of Diclofenac sodium using direct compression after incorporating super disintegrant such as cross linked carboxy methyl cellulose, sodium starch glycolate and cross linked crospovidone in different concentrations and evaluated the effect of their concentrations on the characteristics of fast dissolving tablets mainly in terms of disintegration time and dissolution rate.

Mutasem *et al.,*[40] was studied the effect of increase in Epinephrine in fast disintegrating tablets. They used microcrystalline cellulose and L-hydroxy propyl cellulose as a diluent in the ratio (9:1) and direct compression was employed in the preparation of the tablets. Result shown that linear increase in compression force resulted in linear increase in disintegration and wetting time of formulations without epinephrine and exponential increase in disintegration time and wetting time for tablets containing Epinephrine.

Mishra *et al.,*[41] was assessed the suitability of spray dried excipient base in the formulation of oral disintegrating tablets of Valdecoxib and Metoclopramide. Superdisintegrants (such as Ac-Di-Sol, Kollidon CL, sodium starch glycolate), diluent (mannitol) along with sweetening agent (aspartame) were used in the formulation of tablets. Using the same excipient, the tablets were prepared by direct compression and were evaluated in the similar way. Maximum drug release and minimum disintegrating time were observed with Kollidon CL excipient base as compared to tablets prepared by direct compression, showing the superiority of the spray dried excipient base technique over direct compression technique.

Chandrasekhar *et al.,*[42] was reported preparation and evaluation of Nimesulide dispersible tablet using primo gel as dispersing agent with starch, lactose and dicalcium phosphate as diluents. The tablets were prepared by wet granulation method and compared with commercial dispersible tablets. The formulation with starch and lactose as diluents showed

fast and rapid dissolution than conventional tablets; whereas the tablets with dicalcium phosphate as diluent showed less dissolution rate.

Nayak and Gopala[43] had formulated fast dissolving tablets of Promethazine theocholate. They used three different methods for the preparation of tablets, effervescent melt method using citric acid, sodium bicarbonate. Second method was by grinding microcrystalline cellulose and mannitol and compression. Third method was by adding sugars like high mould ability and low mould ability sugars. They confirmed that effervescent are better forms for mouth feel and better release.

Bhagawati *et al.,*[44] had formulated dispersible tablet of Cefixime with various disintegrates like croscarmellose sodium, sodium starch glycollate, crospovidone and using starch and PVP K30 as binders. They used direct compression as the method of preparation of tablets. Even though the mean disintegration time decrease with sodium starch glycollate and Crospovidone. In comparison with croscarmellose sodium it is impediment they concluded that croscarmellose sodium is best of the three.

Chaudhari *et al.,*[45] had masked the bitter taste of the drug by complexing with eudragit E100 at different concentrations of 1:1 to 1:10. Mouth dissolving tablets were prepared by using Ac-Di-Sol and polyplastadone as Superdisintegrants. They used direct compression method for preparation of tablets. They found that all the formulations showed faster release compared to marketed products that show 20 min for the 100% all formulations showed 81% to 87% release of the drug in first 2 minutes. Stability studies showed that there is a slight increase in disintegration time and decreased in dissolution may be due to formation of lumps of eudragit.

Adel *et al.,*[46] was prepared Tenoxicam fast disintegrating tablets with solid disposition on super disintegrant and used camphor as sublimating agent to prepare the porous structure. They found the tablets with drug excipient ratio 1:9 with camphor showed fastest dissolution rate. The in vivo studies showed that the formulation having sodium starch glycollate have higher dissolution when prepared with camphor sublimation

Sreenivas *et al.,*[47] was prepared Ondansetron hydrochloride mouth disintegrating tablets using various disintegrant like crospovidone, croscarmellose sodium, pre-gelatinized starch, sodium starch glycolate and low-substituted hydroxyl propyl cellulose (L-HPC) in 5% and 10% concentrations and by direct compression method. Result shows that tablets containing 10% disintegrant concentration of crospovidone and croscarmellose sodium were best for Ondansetron hydrochloride mouth disintegrating tablets.

Avinash *et al.,*[48] had formulated highly porous mouth dissolving tablets of Domperidone by using meltable binder polyethylene glycol 4000, mannitol, Camphor, ammonium bicarbonate that sublimes rapidly. The later is removed from the tablets by sublimation process after compressing. Two of the formulations having 40% w/w of ammonium bicarbonate and 20% of camphor respectively emerged to be the most satisfactory exhibiting the disintegrating time of 19.66±1.53 seconds and 21.33± 1.16 seconds and other parameters were found to be satisfactory.

Patel *et al.,*[49] was selected crospovidone from three super disintegrant as the prime study by considering wetting time and disintegrating time. In this work Rofecoxib tablets were prepared by wet granulation method. They conducted optimizing the concentration of crospovidone and concluded 10 % concentration as the best concentration for preparing fast disintegrating tablets. To these results 3^2 factorial design was employed taking concentration of crospovidone and mannitol as independent variable and wetting time and disintegration time as the dependent variables. The best formula was compared with two marketed formulations and the obtained formula showed better dissolution than marketed products.

Mahajan *et al.,*[50] was prepared mouth dissolving tablets of Sumatriptan sulphate by using disintegrant sodium starch glycolate, carboxy methyl cellulose and treated agar by direct compression. The tablets disintegrate by In vitro and In vivo methods in 10 minutes. The formulation containing combination of sodium starch glycolate and carboxymethyl cellulose was found to give the best results when compared to carboxy methyl cellulose and agar.

Patel *et al.,*[51] had formulated tablets of Piroxicam with PVP K30 and sodium lauryl sulphate with a view to increase its water solubility. Sodium lauryl sulphate is used in solid dispersion

with PVP K30 by solvent evaporation method. This solid dispersion was converted into tablets by using different disintegrating agents like sodium starch glycollate and crospovidone. 3^2 factorial designs were applied for the study and they found increase in dissolution with the super disintegrant concentration.

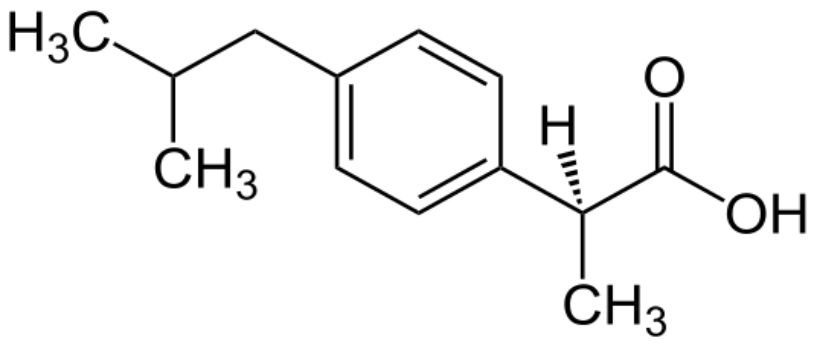
Kuchekar *et al.,*[52] was attempted to make mouth-dissolving tablets of Salbutamol sulphate and they employed 2^n factorial design to select the super disintegrant from croscarmellose sodium, treated agar and sodium starch glycollate for the formulations preparations. Tablet was prepared by direct compression method. Result shown that formulations containing sodium starch glycolate showed excellent release compared to other formulations. Even at the lower concentrations.

Chowdary and Hemavathi [53] had reported the formulation of Ibuprofen dispersible tablets by employing potato starch, primo gel, microcrystalline cellulose and pre-gelatinized starch. Tablets formulated employing primo gel as internal and external disintegrant and tablets formulated employing potato starch as internal disintegrant and primo gel and pre-gelatinized starch as external disintegrant fulfilled the entire official and other requirements of dispersible tablets. These tablets also gave rapid and higher dissolution rate then the formulated as well as conventional tablets.

3.2 DRUG PROFILE:

Name of the drug: Dexibuprofen

Chemical structure:



Chemical name: (2*S*)-2-[4-(2-methylpropyl)phenyl]propanoic acid

Empirical formula: $\mathbf{C_{13}H_{18}O_2}$

Molecular weight: 206.28082 g/mol

Introduction[54]

Dexibuprofen is a non-steroidal anti-inflammatory agent (NSAIA) with analgesic and antipyretic properties. It is prescribed for moderate to severe pain such as dysmenorrhea, toothache, osteoarthritis.

Physical properties[55]

Dexibuprofen occurs as a white, bitter powder. It melts at 76°C. It is sparingly soluble in water and freely soluble in methanol, ethanol, Isopropyl alcohol, Ethyl acetate. Dissociation constant pKa of Dexibuprofen is 4.91.

Stereochemistry[56]**:** Dexibuprofen, S(+)-ibuprofen, is a pharmacologically active form and is more potent than ibuprofen, which has equal quantities of R(−)- and S(+)-enantiomers

BCS Class: II (low soluble and highly permeable)

Stability: Stable under ordinary conditions.

Analytical methods[55]

A number of analytical methods have been reported for the analysis of Dexibuprofen. These include Ultra violet Spectrophotometric methods, HPLC methods, GC methods and GC/MS method.

Mechanism of Action[55]

Dexibuprofen is a non-selective inhibitor of cyclooxygenase, an enzyme involved in prostaglandin synthesis via the arachidonic acid pathway. Its pharmacological effects are believed to be due to inhibition cyclo-oxygenase-2 (COX-2) which decreases the synthesis of prostaglandins and formation of thromboxanes involved in mediating inflammation, pain, fever and swelling. Antipyretic effects may be due to action on the hypothalamus, resulting in an increased peripheral blood flow, vasodilation, and subsequent heat dissipation. Inhibition of COX-1 is thought to cause some of the side effects of Dexibuprofen including GI ulceration.

Pharmacokinetics[57]

Absorption

Bioavailability

Rapidly absorbed from the GI tract following oral administration; bioavailability averages approximately 80%.Peak plasma concentrations usually occur within 2 to2.1 hours after oral administration.

Distribution

Dexibuprofen is distributed in the body by binding to human plasma proteins at therapeutic concentrations

Plasma Protein Binding

Highly bound to plasma protein (90-99%) and site II of purified albumin, binding appears to be saturable and becomes non-linear at concentrations exceeding 20 mcg/ml.

Metabolism

Extensively metabolized in the liver by oxidation to 2 inactive metabolites: (+)-2[4´-(2-hydroxy-2-methylpropyl)phenyl]propionic acid and (+)-2-[4´-(2-carboxypropyl)phenyl]propionic acid. Cytochrome P450 2C9 is the major catalyst in the formation of oxidative metabolites. Oxidative metabolites may be conjugated to glucuronide prior to excretion.

Elimination Route

Dexibuprofen is rapidly metabolized and eliminated in the urine.

Half-life

2-4 hours.

Pharmacodynamics:

Dexibuprofen is a nonsteroidal anti-inflammatory agent (NSAIA) or nonsteroidal anti-inflammatory drug (NSAID), with analgesic and antipyretic properties. Dexibuprofen has pharmacologic actions similar to those of other prototypical NSAIAs, which are thought to act through inhibition of prostaglandin synthesis.

Pharmacological effects[58]

Dexibuprofen inhibits prostaglandin synthesis and formation of thromboxanes via blockade of cyclo-oxygenase (COX) enzymes. Dexibuprofen inhibits both COX-1 and COX-2 synthesis.

Indication:

For symptomatic treatment of rheumatoid arthritis, juvenile rheumatoid arthritis and osteoarthritis. May be used to treat mild to moderate pain and for the management of dysmenorrhea. May be used to reduce fever. Has been used with some success for treating ankylosing spondylitis, gout and psoriatic arthritis. May reduce pain, fever and inflammation of pericarditis.

Contraindications:

- Hypersensitivity to Dexibuprofen to any other NSAID or to any of the excipients.
- Active or suspected gastrointestinal ulcer or history of recurrent gastrointestinal ulcer Gastrointestinal bleeding or other active bleedings or bleeding disorders.
- Active Crohns disease or active ulcerative colitis.
- Severe heart failure.
- Severe impaired hepatic function.

- Haemorrhage diathesis & other coagulation disorders or patients receiving anticoagulant therapy.
- Third trimester pregnancy.

Use with caution in:

- Elderly people.
- History of disorders affecting the stomach or intestines.
- Inflammatory bowel disease such as Crohn's disease or ulcerative colitis.
- Alcoholism.
- Decreased kidney function.
- Decreased liver function.
- Heart failure.
- High blood pressure (hypertension).
- History of asthma.
- History of allergies.
- Diseases affecting connective tissue, e.g. systemic lupus erythematosus.
- People with blood clotting disorders, e.g. haemophilia, or taking anticoagulant medicines.

Precautions in:

- People in whom aspirin or other NSAIDs, e.g. ibuprofen, cause allergic reactions such as asthma attacks, itchy rash (urticaria), nasal polyps, nasal inflammation (rhinitis) or swelling of the lips, tongue and throat (angioedema).
- Active peptic ulcer or bleeding from the gut.
- People who have had recurrent peptic ulcers or bleeding from the gut (two or more episodes).
- People who have experienced bleeding or perforation of the gut as a result of previous treatment with an NSAID.
- Flare-ups of Crohn's disease.
- Flare-ups of ulcerative colitis.
- Severe heart failure.
- Severely decreased kidney and liver functions.
- Third trimester of pregnancy.

Pregnancy and lactation:

Certain medicines should not be used during pregnancy or breastfeeding. However, other medicines may be safely used in pregnancy or breastfeeding providing the benefits to the mother outweigh the risks to the unborn baby. Always inform your doctor if you are pregnant or planning a pregnancy, before using any medicine.

- This medicine should not be used in the third trimester of pregnancy, as it may delay labour, increase the length of labour and cause complications in the newborn baby. It should only be used in the first and second trimesters if the potential benefit outweighs any potential risk to the foetus. Some evidence suggests that NSAIDs should also be avoided by women attempting to conceive, as they may temporarily reduce female fertility during treatment and may also increase the risk of miscarriage or malformations. Seek medical advice from your doctor.
- This medicine may pass into breast milk, but in such small quantities that it is unlikely to harm the baby if the dose is low and treatment is short. However, as with all medicines, seek medical advice from your doctor before breastfeeding while taking this medicine.

Side effects:

Medicines and their possible side effects can affect individual people in different ways. The following are some of the side effects that are known to be associated with this medicine. Just because a side effect is stated here, it does not mean that all people using this medicine will experience that or any side effect.

- Disturbances of the gut such as nausea, vomiting, diarrhoea, indigestion or abdominal pain.
- Headache.
- Dizziness.
- Balance disorders involving the inner ear (vertigo).
- Drowsiness.
- Bleeding from the stomach or intestine.
- Stomach or duodenal ulcer.
- Retention of water in the body tissues (fluid retention), resulting in swelling (oedema).
- Sensation of ringing or other noise in the ears (tinnitus).
- Visual disturbances.
- Confusion.
- Depression.

- Abnormal reaction of the skin to light, usually a rash (photosensitivity).
- Allergic reactions such as severe skin rashes, swelling of the lips, tongue and throat (angioedema) or narrowing of the airways (bronchospasm).
- Kidney, liver or blood disorders.

Drug Dosing:

- The recommended dose of Dexibuprofen is 600-900 mg/day in 2-3 divided doses for pain and inflammation associated with musculoskeletal and joint disorders; Dysmenorrhoea in adult.
- Maximum single dosage is 400mg Dexibuprofen
- Dose may be increased up to 1200 mg Dexibuprofen per day in pts with acute conditions or exacerbations
- Maximum daily dose is 1200mg in case of mild to moderate hepatic conditions.

3.3 EXCIPIENTS PROFILE:

Excipients:

Substances, other than the active ingredient, which have been appropriately evaluated for safety and are included in a drug delivery system to provide support.

The excipients used must have following characteristics-

- They must be stable both physically, chemically and must be biologically inactive.
- It must be free from microbial contamination
- Excipients used in tablet formulation must be accepted by regulatory agencies and should meet the entire current regulatory requirement.

Excipients used are :

- Microcrystalline cellulose
- Crospovidone
- Croscarmellose sodium
- Sodium starch glycollate
- Aspartame
- Colloidal silicon dioxide

- Magnesium stearate

MICROCRYSTALLINE CELLULOSE[59]

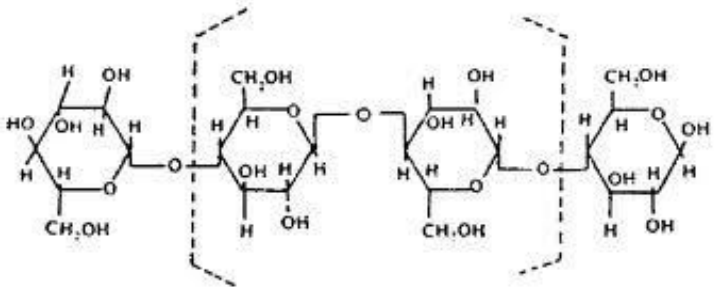
Synonyms : Avicel PH, Celex, cellulose gel; Celphere; CeoulusCrystalline cellulose; E460; Emcocel; Fibrocel; Pharmacel; Tabulose; Vivapur

Chemical names : Cellulose

Empirical formula : $(C_6H_{10}O_5)_n$ n=220

Molecular weight : 36,000(approx)

Structural formula :



Description : Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odourless, tasteless, crystalline powder composed of porous particles

Functional category : Adsorbent; suspending agent; tablet and Capsule diluent; tablet disintegrant.

Uses : Adsorbent, Anti-adherent, Tablet disintegrant, Tablet binder.

Applications : Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations.

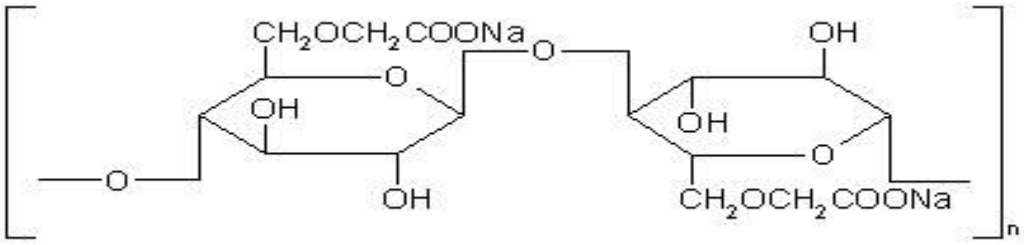
Microcrystalline cellulose is also used in cosmetics and food products.

CROSCARMELLOSE SODIUM[60]

Synonyms : Ac-Di-Sol, Crosslinkedcarboxymethylcellulose sodium, modified cellulose gum, Nymcell ZSX, Primellose, Solutab.

Chemical name : Cellulose sodium salt of carboxymethyl ether.

Structural formula :



Functional category : Tablet and capsule disintegrant.

Description : Croscarmellose sodium occurs as an odorless, white Colored powder.

Applications in pharmaceutical formulation or technology:

It swells 4-8 folds in 10 seconds. The cellulose derivative swells in two dimensions radially. In tablet formulations, croscarmellose sodium may be used in both direct compression and wet granulation processes. When used in wet granulation croscarmellose sodium is added to in both the wet and dry stages of the process so that wicking and swelling ability can both be utilized.

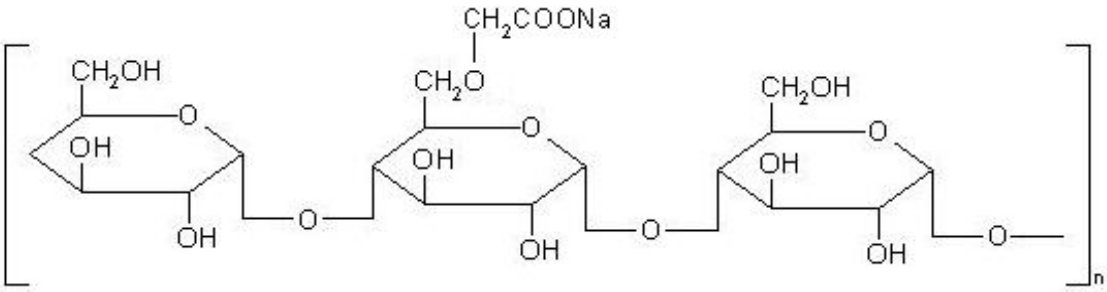
SODIUM STARCH GLYCOLLATE[61]

Synonym : Carboxymethyl starch sodium salt, Explotab, Primojel,

Viva-star P.

Chemical name : Sodium carboxy methyl starch.

Chemical structure :



Description : Sodium starch glycolate is a white to off-white, free flowing, practically tasteless, odorless powder. It consists of oval or spherical granules, 30-100μm in diameter. The diameter of the smaller granules ranging from 10-35 mcg.m.

Functional category : Tablet and Capsule Disintegrant

Solubility : Sparingly soluble in ethanol (95%), practically Insoluble in water. At a concentration of 2% w/v in cold water and settles in the form of a highly hydrated layer.

Stability and storage : Tablets prepared with SSG have good storage Properties. It is stable and should be stored in a closed container to protect it from wide variations in humidity and temperature to avoid caking. The physical properties of SSG remain unchanged up to 4 years if stored at moderate temperatures and humidity conditions.

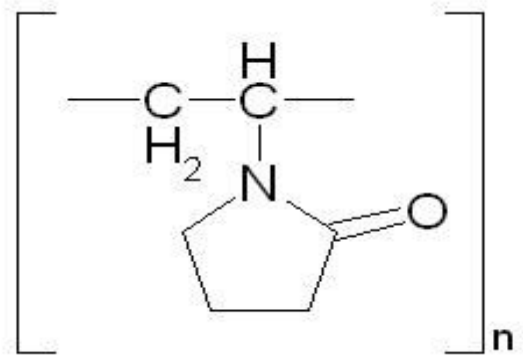
Applications in pharmaceutical formulation:

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in tablet and capsule formulations. It is commonly used in tablets prepared by either direct compression or wet granulation process. The usual concentration employed in a formulation is between 2-8%. Disintegration occurs by rapid uptake of water followed by rapid and

enormous swelling. Increasing the tablet compression appears to have no effect on disintegration time.

CROSPOVIDONE[62]

Structural formula:



Synonyms : Kollidon CL, Kollidon CL–M, Polyplasdone-XL, Polyplasdone XL-10

Chemical Name : 1- ethenyl – 2- pyrrolidinone homopolymer

Nonproprietary Name: BP – Crospovidone
PhEur -Crospovidonum
USP NF – Crospovidone.

Description : Crospovidone is white to creamy white finely divided, free flowing practically tasteless / nearly odorless, hygroscopic powder.

Solubility : Practically insoluble in water and most organic solvents.

Functional Category : Tablet disintegrant.

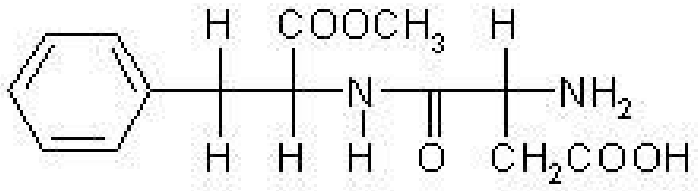
Application in Pharmaceutical Formulation:

Crospovidone is water insoluble tablet disintegrant and used at 2-8% concentration in tablets prepared by direct compression / wet and dry granulation methods. It exhibits high capillary activity and pronounced hydration capacity. Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer with the technique of co-evaporation. It can also used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to

crospovidone in the presence of a suitable solvent and solvent is evaporated. This technique results in faster dissolution rate.

ASPARTAME[63]

Structural formula:



Synonyms:

Aspartyl phenyl amine Methyl Ester, Canderel, NutraSweet, Sancta, Tri-Sweet.

Functional category:

Sweetening agent.

Applications:

It is used as an intense sweetening agent in tablets powder mixes and vitamin preparations. It enhances flavor systems, can be used to mask some unpleasant taste, and has sweetening power of 180-200 times that of sucrose.

Description:

It occurs as white, almost odorless crystalline powder.

Solubility:

Slightly soluble in ethanol (95%), sparingly soluble in water. Solubility increases at higher temperature and more acidic pH

Stability:

It is stable in dry conditions. In presence of moisture, hydrolysis occurs. Degradation also occurs during prolonged heat treatment.

Storage conditions:

Bulk material should be kept in a well-closed container and stored in a cool dry place.

Incompatibilities:

Incompatible with dibasic calcium phosphate & also with magnesium stearate.

Safety:

The WHO has set an acceptable daily intake of 40mg/kg body weight.

COLLOIDAL SILICON DIOXIDE[64]

Synonyms:

Aerosil, Cab-O-Sil, Cab-O-Sil M-5P, colloidal silica, fumed silica, light anhydrous silicic acid, silicic anhydride, silicon dioxide fumed, Wacker HDK.

Chemical Name and CAS Registry Number:

Silica [7631-86-9].

Empirical Formula and Molecular Weight:

SiO_2 - 60.08.

Functional Category:

Adsorbent ant caking agent, emulsion stabilizer, Glidant, suspending agent, tablet disintegrant, thermal stabilizer, viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology:

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products. Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting. Colloidal silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations.

Description:

It is a light, loose, bluish-white colored, odorless, tasteless, no gritty amorphous powder.

Incompatibilities:

Incompatible with diethylstilbestrol preparations.

MAGNESIUM STEARATE[65]

Synonyms:

Magnesium octadecanoate, Octadecanoic acid, Magnesium salt, Stearic acid, Magnesium salt.

Chemical Name and CAS Registry Number:

Octadecanoic acid magnesium salt [557-04-0]

Empirical Formula and Molecular Weight:

$C_{36}H_{70}MgO_4$ - 591.34

Structural Formula:

$[CH_3 (CH_2)_{16}COO]_2 Mg$

Functional Category:

Tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology:

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% to 5.0% w/w. It is also used in barrier creams.

Description:

Magnesium stearate is a very fine, light weight, precipitated or milled, impalpable powder of low bulk density, having a faint odor of Stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Incompatibilities:

Incompatible with strong acids, alkali's, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins and most alkaloidal salts.

4. METHODOLOGY

4.1. MATERIALS AND EQUIPMENTS

The following drug, excipient and chemicals were used for the formulation of ODTs.

Table 2 : List of Excipients and Chemicals

Sr. No.	Name	Supplier of Materials	Function
1	Dexibuprofen	Glochem Industries Ltd.	Anti-inflammatory agent
2	Microcrystalline cellulose	Glochem Industries Ltd.	Diluent
3	Croscarmellose Sodium	Loba chemicals , Mumbai, India	Super Disintigrant
4	Sodium Starch Glycollate	Meggle, Germany	Super Disintigrant
5	Crospovidone XL 10	Colorcon Asia Pvt. Ltd. Goa, India	Super Disintigrant
6	Aspartame	S.D.Fine Chemicals Ltd., Mumbai, India	Sweetner
7	Colloidal Silicon Dioxide (Aerosil 200)	Fine chemicals, Mumbai, India	Flow improver
8	Magnesium Stearate	Meggle, Germany	Lubricant

Table 3 : List of Equipments

Sr. No.	Equipments	Manufacturers
1	Weighing balance	Mettler Toledo (PG 403-S)
2	pH meter	Thermo electron corporation
3	Mechanical stirrer	Remi
4	Halogen moisture balance	Mettler Toledo
5	Bulk Density Tester (USP)	Electrolab (ETD -1020)
6	Multi-station tablet compression machine	Cadmach
7	Hardness tester	Vankel (VK 200)
8	Friability tester	Electrolab (EF-1W)
9	Vernier caliper scale	Mitutoyo
10	Malvern particle size analyzer	Malvern
11	Stability chambers	Thermolab
12	Disintegration tester	ED-2L Electrolab, Mumbai, Ind
13	Dissolution test apparatus	Labindia DS 8000
14	UV Spectrophotometer	1700, Shimadzu, Japan
15	Melting point apparatus	Elico Ltd

4.2. PREFORMULATION STUDY[66,67]

Preformulation studies are the first step in the rational development of dosage form of a drug substance. The objective of preformulation studies are to develop a portfolio of information about the drug substance, so that this information useful to develop formulation. Preformulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipient.

Preformulation investigations are designed to identify those physicochemical properties and excipient that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product.

Followings test are performed for the Preformulation study.

1. Organoleptic characteristics.
2. Solubility of drug.
3. Particle size distribution.
4. Physico-mechanical characterization.
5. Moisture content.
6. Compatibility study.
7. Drug potency calculation.

1) Organoleptic Characteristics: [66]

The color, odour and taste of the drug were characterized and recorded using descriptive terminology.

2) Solubility: [66]

The solubility of Dexibuprofen was determined as per BCS. The solubility was checked in 250 ml of 0.1N HCl and buffers within pH range 2 – 8 and in water. The highest amount of dose was accurately weighed and transferred in individual volumetric flask containing different solutions and sonicate for 30 minutes.

Table 4 : Solubility studies

Descriptive term	**Part of solvent required for one part of Solute**
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10000
Practically insoluble or insoluble	Greater than or equal to 10000

3) <u>Particle size distribution:</u> [66]

By Malvern master seizer:

For many active substances, particle size has an impact on powder flow; content uniformity and drug dissolution. In order to assure consistent product quality, the particle size of the Dexibuprofen has been characterised. The particle size analyzed by Malvern master seizer is based on the principle of light scattering. The particles can be analyzed by two methods

1. Dry method and
2. Wet method

In present study, the particles size was determined using dry method.

4) Physico-mechanical characterization [66]

- **Bulk Density**:

It refers to packing of particles. Bulk density is used to determine the amount of drug that occupies the volume in g/ml.

Procedure: Weighed quantity of Dexibuprofen was transferred into 100 ml measuring cylinder without tapping during transfer. The volume occupied by drug was measured. Bulk density was measured by using formula

$$\rho_i = m / V_i$$

Where, m = mass of the blend

V_i = untapped volume

- **Tapped density:**

Weighed quantity of drug was taken into a graduated cylinder. Volume occupied by the drug was noted down. Then the cylinder was subjected to 500, 750 &1250 taps in tap density apparatus (Electro Lab USP II). According to USP, The blend was subjected for 500 taps. % Volume variation was calculated and subjected for additional 750 taps. % Variation is calculated.

$$\rho_t = m/V_t$$

Where, V_t is tapped volume

- **Carr's Index (Compressibility):**

The compressibility index and Hausner ratio are measures of the property of powder to be compressed. The packing ability of drug was evaluated from change in volume, which is due to rearrangement of packing occurring during tapping. It was indicated as Carr's compressibility index was calculated as follows.

Carr's index = [Tapped density - Bulk density/Tapped density] X 100

- **Hausner Ratio:**

It is measurement of frictional resistance of the drug .The ideal range should be 1.2-1.5. It was determined by the ratio of tapped density and bulk density

Hausner Ratio = Tapped density / Bulk density

- **Angle of Repose:**

It is defined as the maximum angle that can be obtained between the free standing of powder heap and horizontal plane, which is given by the equation:

$$\theta = \tan^{-1} h/r$$

Where, θ = Angle of repose.

h = Height of powder heap.

r = Radius of the powder cone.

Procedure: Weighed quantity of the drug was passed through a funnel kept at a height 2 cm from the base. The powder is passed till it forms a heap and touches the tip of the funnel. The radius was measured and angle of repose was calculated by using above formula.

Table 5 : Interpretation of powder flow

Flow Character	Compressibility Index (%)	Hausner Ratio	Angle of Repose (θ)
Excellent	≤ 10	1.00–1.11	25-30
Good	11–15	1.12–1.18	31-35
Fair	16–20	1.19–1.25	36-40
Passable	21–25	1.26–1.34	41-45
Poor	26–31	1.35–1.45	46-55
Very poor	32–37	1.46–1.59	56-65
Very, very poor	> 38	> 1.60	> 66

5) Moisture content:[67]

Moisture content was determined by halogen moisture analyzer. The Halogen moisture Analyzer works along the lines of the thermo gravimetric principle, i.e. the

sample's starting weight was recorded, and then a halogen radiator dries it while an integrated balance continuously records the sample weight. The total loss in weight was interpreted as the moisture content. Drug should have moisture content not more than 0.5 % w/w.

6) Drug-Excipients Compatibility Study[67]

Protocol for drug-excipient compatibility

(a) Drug: Excipient Ratio:

Drug and excipient were taken in the ratios of 1:5

(b) Storage condition:

1. Initial sample at room temperature.
2. 40°C/75 % RH for 4 weeks.

(c) Test to be performed:

1. Physical observation.

Procedure

Dexibuprofen and excipient were to be thoroughly mixed in predetermined ratio of 1:5 and passed through the 40# sieve. The blend was to be filled in transparent glass vials and closed with gray rubber stoppers and sealed with aluminum and kept into condition at 40°C/75 % RH for 4 week. Similarly Dexibuprofen was also subjected to same condition and time period as that of sample.

Physical observation:

Physical observation of each sample was carried out every week, for any color change or lumps formation. No color change or lumps observed in any of the preformulation sample kept for accelerated preformulation stability.

FT-IR:

Dexibuprofen and excipients are subjected to FT-IR spectral analysis. The drug was Compatible with excipients since no significant changes were observed in intensity and position of the peaks in the spectra. The results are shown in graph.

4.3. PREPARATION OF STANDARD CALIBRATION CURVE:

Preparation of Phosphate buffer (pH 6.8)

Take 0.94g of NaOH and 6.845g of KH_2PO_4 in 1000ml volumetric flask, and made upto the volume with distilled water to 1000 ml.

Preparation of Standard Stock Solution of Dexibuprofen

Transfer an accurately weighed quantity of about 10 mg of Dexibuprofen in working standard to a 10 ml volumetric flask. Add about 5 ml of pH 6.8 Phosphate buffer and sonicate to dissolve. Make volume up to the mark with pH 6.8 Phosphate buffer.

Spectrophotometric scanning of Dexibuprofen

λmax was determined by subjecting the stock solution to UV Spectrophotometry between the wave lengths 200- 400 nm which gave a highest peak i.e. λmax at 221 nm.

Preparation of working solution

From standard stock solution respective concentrations of 3,6,9,12,15 and 18 µg/ml were prepared and analyzed by using UV Spectrophotometer at λmax 221 nm and results were recorded. The calibration graph was plotted by taking concentration an x-axis and absorbance on y-axis.

Table 6 : Calibration Curve for Dexibuprofen

Sr. No.	Concentration(µg/ml)	Absorbance at 221nm
1	0	0
2	3	0.158
3	6	0.316
4	9	0.468

5	12	0.597
6	15	0.742
7	18	0.909

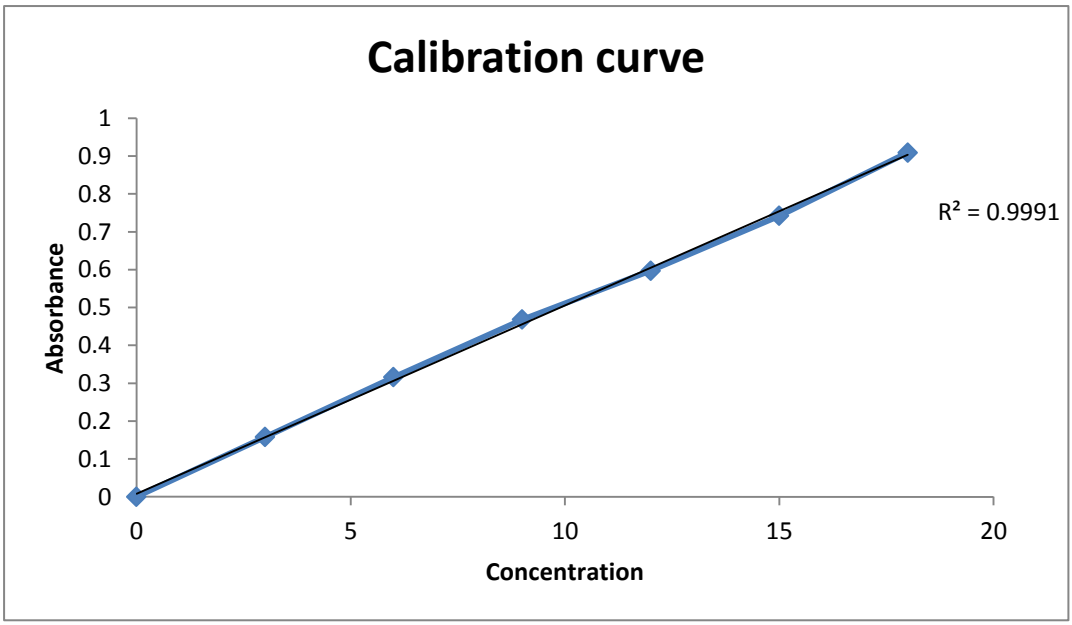


Figure 8 : Calibration Curve for Dexibuprofen

4.4 STRATEGIES FOR DEVELOPMENT OF ORODISPERSIBLE TABLET

FORMULATION OF TABLETS:

Sr. No	Ingredients	F1 (mg/tab)	F2 (mg/tab)	F3 (mg/tab)	F4 (mg/tab)	F5 (mg/tab)	F6 (mg/tab)
1.	Dexibuprofen	100	100	100	100	100	100

2.	Microcrystalline cellulose	91	91	91	87	87	87
3.	Crospovidone	4	-	-	8	-	-
4.	Croscarmellose Sodium	-	4	-	-	8	-
5.	Sodium Starch Glycollate	-	-	4	-	-	8
6.	Aspartame	2	2	2	2	2	2
7.	Colloidal Silicon Dioxide	1.5	1.5	1.5	1.5	1.5	1.5
8.	Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5
	Net Total	**200.00**	**200.00**	**200.00**	**200.00**	**200.00**	**200.00**

Table 7 : Composition of formulation batch F1 to F6

Table 8 : Composition of formulation batch F7 to F12

Sr. No	**Ingredients**	F7 (mg/tab)	F8 (mg/tab)	F9 (mg/tab)	F10 (mg/tab)	F11 (mg/tab)	F12 (mg/tab)

1.	Dexibuprofen	100	100	100	100	100	100
2.	Microcrystalline cellulose	83	83	83	79	79	79
3.	Crospovidone	12	-	-	16	-	-
4.	Croscarmellose Sodium	-	12	-	-	16	-
5.	Sodium Starch Glycollate	-	-	12	-	-	16
6.	Aspartame	2	2	2	2	2	2
7.	Colloidal Silicon Dioxide	1.5	1.5	1.5	1.5	1.5	1.5
8.	Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5
	Net Total	**200.00**	**200.00**	**200.00**	**200.00**	**200.00**	**200.00**

4.5 PROCEDURE:

Direct Compression Method

- Weigh the ingredients Dexibuprofen, Diluents (Microcrystalline cellulose PH 102) and superdisintegrant (Sodium Starch Glycollate, Croscarmellose Sodium, Crospovidone) and sift individually through 40# sieve and Colloidal Silicon Dioxide, Sweetener, Lubricant through 60# sieve.
- Mix all the ingredient in poly bags for 5 min.
- Above blend passed through 40 # mesh and mix it.
- Lubricated blend was compressed into tablets using 6.35mm Flat Face Round edged punch set using a eight station tablet press.
- Compression was carried out using "D" tooling punches sets.

4.6 EVALUATION

Prepared Orodispersible tablets were evaluated for the following parameters.

a. Physical characterization

- Physical appearance
- Hardness, Thickness.
- Disintegration time
- Friability.
- Water absorption ratio
- Wetting time
- Weight variation.
- Dissolution *(In-Vitro* release)

b. Stability study of optimized formulation as per ICH

A) Physical Characterization[67]

- **Physical appearance:[67]**

The general appearance and elegance of tablet was identified visually, which include tablet size, shape, color, presence or absence of an odor, taste, surface texture and avoid of sticking etc.

- **Hardness:[67]**

Tablets require certain amount of strength or hardness, to withstand mechanical shocks of handling in manufacture, packaging, and shipping. The most widely used apparatus to measure tablet hardness (crushing strength) is the Schleuniger hardness tester.

Method: Ten tablets were randomly selected and hardness was measured in Schleuniger hardness tester. The average was taken as hardness of the tablet.

- ***In vitro* disintegration test:**[67]

In vitro disintegration time was measured using USP disintegration test apparatus. Randomly six tablets were selected from each batch for disintegration test. Disintegration test was performed in 900ml distilled water at 37±0.5 °C temperature and at the rate of 30±2 cycles/min.

- **Thickness:** [67]

Ten Tablets were selected randomly from individual formulations and thickness was measured by using vernier caliper scale, which permits accurate measurement.

- **Friability:**[67]

Friability is related to the ability of tablet to withstand both shocks and abrasion without crumbling during manufacturing, packing, transportation and consumer handling. Friability can be evaluated by means of friability test apparatus (The Roche friabilator). Compressed tablets that loose less than 0.5% to 1.0% in weight are generally considered acceptable.

Method: Ten tablets were weighed (initial wt.) and then transfer into Rocha friabilator. It was subjected to 100 revolutions in 4 minutes. The tablets were dedusted and reweighed (final wt). These two weights were applied to following formula and friability was calculated.

$$\% \text{ Friability} = \frac{\text{(Initial Weight – final weight)}}{\text{(Initial weight)}} \times 100$$

- **Water absorption ratio:**[68]

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of distilled water. A tablet was put on the paper and time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, was determined using equation:

$$R = \frac{(Wa - Wb)}{Wb} \times 10$$

Where, Wb = weight of the tablet before water absorption

Wa = weight of the tablet after water absorption

- **Wetting time:**[67]

For measurement of wetting time five circular tissue papers of 10 cm diameter are placed in a petri dish with a 10 cm diameter. 10ml of water-containing Eosin, a water-soluble dye, is added to petri dish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

- **Weight variation:**[67]

Twenty tablets were taken randomly, weigh individually and average weight was determined. The individual tablet weight was compared with average tablet weight.

Table 9 : Weight variation of tablets as per USP

Avg. Weight(mg)	Maximum % difference allowed
≤ 130	± 10
130-324	± 7.5
≥ 324	± 5

- ***In vitro* dissolution study**[69]

Medium : 900 ml; Phosphate buffer pH 6.8

Apparatus : USP-II (paddle)

RPM : 50

Temperature : 37°C ± 0.5°C

Time : 60 minutes

Preparation of dissolution medium (Phosphate buffer pH6.8) :

Take 0.94g of NaOH and 6.845g of KH_2PO_4 in 1000ml volumetric flask, and made upto the volume with distilled water to 1000 ml.

Test solution: Set the dissolution parameters of the instrument as mentioned above. Place one tablet each in six different baskets and operate the apparatus exactly for specified time. At the end of specified time, withdraw about 10 ml of solution from a zone midway between the surface of the dissolution medium and top of the basket, not less than 1 cm from the bowl wall. Filter the solution through 0.45 µm Millipore HVLP filter; collect the filtrate by discarding first few ml of the filtrate.

Procedure: Measure the absorbance of test sample solution in 1 cm cell or cuvette on UV spectrophotometer (1700 Shimadzu) at 221 nm, using dissolution medium (phosphate buffer pH 6.8) as blank. Then Calculate the quantity as percentage of Drug dissolved or released.

B) <u>Stability Study of Optimized Formulation</u> [70,71]

Stability testing of drug products begins as a part of drug discovery and ends with the demise of the compound or commercial product. FDA and ICH specifies the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human use.

The ICH Guidelines have established that long term stability testing should be done at 25^0C/60% RH; stress testing should be done at 40^0C/75%RH for 6 months. If significant change occurs at these stress condition, then the formulation should be tested at an intermediate condition i.e. 30^0C/65%RH.

Table 10 : ICH guide lines for stability study

Study	Storage condition	Time period
Long term*	25°c±2°C/60% RH±5%RH or 30°c±2°C/65%RH±5% RH	12 month
Intermediate**	30°c±2°c/65% RH±5% RH	6 month

Accelerated	40°c±2°c/75% RH±5% RH	6 month

In the present work stability study was carried out for the optimized formulation for following condition and time period,

- 40° C / 75% RH for 1 month

Then tablets were evaluated for hardness, drug content, and dissolution study and compared with tablets which were evaluated immediately after manufacturing.

5. RESULTS AND DISCUSSION

5.1 PRE-FORMULATION STUDIES:

- **Organoleptic characteristics:**

Table 11 : Organoleptic properties of Dexibuprofen

Properties	Results
Colour	White
Taste	Bitter
Odour	Odorless

- **Solubility:**

Table 12 : Results of solubility study

Sr. No.	Dissolution media 37°C	Solubility(mg/L)
1.	Purified Water	21
2.	0.1N Hydrochloric Acid	15
3.	Acetate Buffer pH 4.5	17
4.	Phosphate Buffer pH 6.8	20
5.	Phosphate Buffer pH 7.4	18

From above data stated that drug is sparingly water soluble.

- **Particle size distribution:**

  By Malvern master seizer, dry method

Table 13 : Dexibuprofen Particle size

Particle size	Results
10 % Particles	< 4 μ
40 % particles	< 10 μ
90 % Particles	< 21 μ

- **Physico-mechanical characterization:**

Table 14 : Dexibuprofen Physico-mechanical properties

Sr. No.	Parameters	Results	Inference
1.	Bulk Density	0.43 gm/ml	-
2.	Tapped Density	0.55 gm/ml	-
3.	Carr's index	21.81 %	Passable
4.	Hausner Ratio	1.27	Passable
5.	Angle of Repose	39.45	Good

Table 15 : Physico- mechanical properties of Formulations

Batch	Bulk Density(g/ml)	Tapped Density(g/ml)	Carr's Index	Hausner's ratio	Angle of Repose(θ)
F1	0.414	0.542	23.616	1.309	40°27’
F2	0.420	0.543	22.65	1.292	39°14’
F3	0.440	0.535	17.757	1.215	38°21’
F4	0.455	0.540	15.74	1.186	35°14’
F5	0.460	0.541	14.97	1.170	33°17’
F6	0.462	0.542	14.760	1.173	32°12’
F7	0.462	0.541	14.602	1.170	33°15’
F8	0.463	0.543	14.732	1.172	32°10’
F9	0.463	0.542	14.57	1.170	32°09’
F10	0.461	0.541	14.78	1.173	32°12’
F11	0.462	0.540	14.44	1.168	31°25’
F12	0.465	0.540	13.88	1.161	31°10’

- **Moisture content:**

Moisture content was determined by halogen moisture analyzer. Drug has moisture content of 0.3 % w/w. which is within limit.

- **Drug potency calculation:**

$$\text{Assay on as is basis} = \frac{\text{Assay} \times (100 - \text{Moisture})}{100}$$

$$= \frac{98.5 \times (100 - 0.3)}{100}$$

$$= 98.20\ \%$$

$$\text{Assay on 100\% basis} = \frac{\text{Assay} \times 100}{\text{Assay on as is basis}} = \frac{98.5 \times 100}{98.20}$$

Assay on 100% basis = 100.3

Flow properties of the Dexibuprofen blend, resistance to particle movement can be judged from the bulk density, tapped density, compressibility index, Hausner's ratio. This measurement gives qualitative and quantitative assessment of internal cohesive and frictional force under low levels of external loading as might be applied in mixing and tabletting. The bulk density was found within the range of 0.414 to 0.465 g/cc . The tapped density was found within the range of 0.535 to 0.543 g/cc. Using the density data, Hausner's ratio and Carr's index was calculated. The Hausner's ratio was found within the ranges of 1.16 to 1.3 which indicates better flowability. The Carr's index was found within the ranges of 13.88 to 23.61 explaining good flow properties.

Drug-Excipient Compatibility Study:

1) Physical observation:

Table 16 : Results for drug-excipient compatibility

Name of Sample	Ratio	Observation		
		Initial	**RT initial**	**40^0/75%RH 4weeks**
Dexibuprofen	--	White powder, free flowing. No aggregates	White powder, free flowing. No aggregates	Whitepowder, free flowing. No aggregates
Dexibuprofen + Microcrystalline cellulose	1:5	Do	No change	No change
Dexibuprofen + Crospovidone	1:5	Do	No change	No change
Dexibuprofen + Croscarmellose Sodium	1:5	Do	No change	No change
Dexibuprofen + Sodium Starch Glycollate	1:5	Do	No change	No change
Dexibuprofen + Colloidal Silicon Dioxide	1:5	Do	No change	No change
Dexibuprofen + Mg. Stearate	1:5	Do	No change	No change
Dexibuprofen + Aspartame	1:5	Do	No change	No change

Compatibility test – FT-IR method:

Dexibuprofen and excipients are subjected to FT-IR spectral analysis. The drug was Compatible with excipients since no significant changes were observed in intensity and position of the peaks in the spectra. The results are shown in graph.

Figure 9 : FT-IR spectra of pure drug of Dexibuprofen

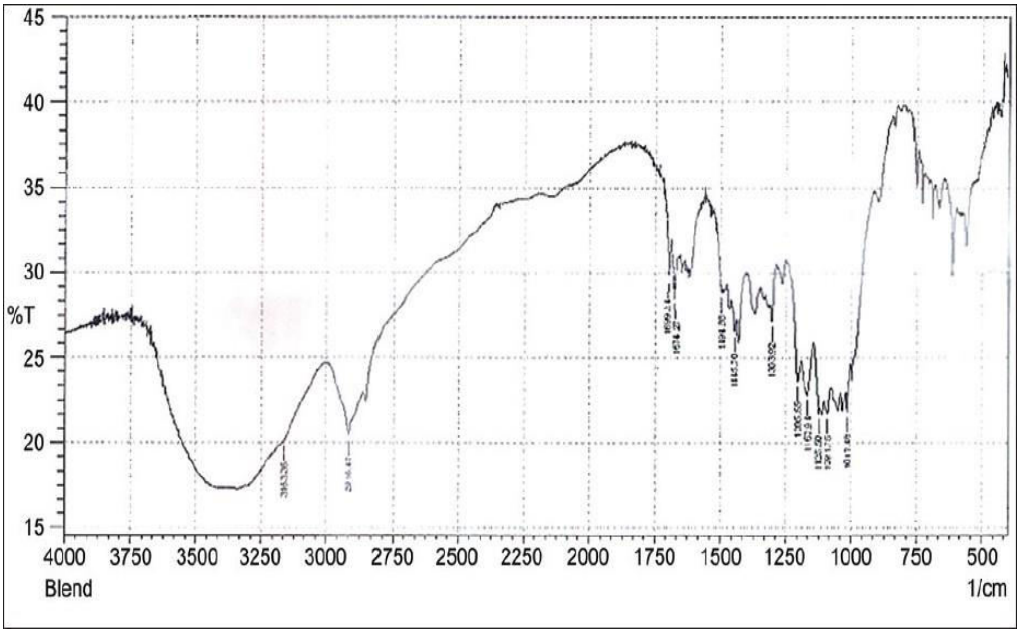
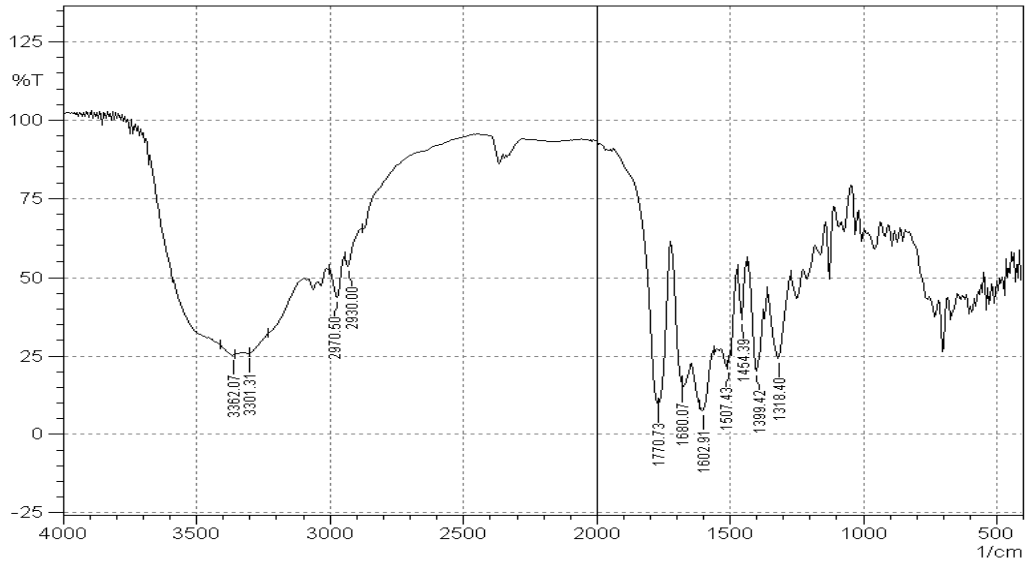


Figure 10 : FT-IR spectra of optimized formulation of Dexibuprofen ODT



These are the compatibility studies showed that there was no chemical change or interaction between drug and selected excipient. Based on physical and chemical compatibility results. The above excipients selected are suitable for formulation development of Dexibuprofen.

5.2 EVALUATION OF ORODISPERSIBLE TABLETS:

Physical Characterization:

Physical appearance:

The physical examination of tablets showed that the tablets were round and circular shape. The studies also indicated that there were no cracks on the tablets. The data indicates that all the formulations were good.

Post compression Parameters:

Tablets were compressed at average wt. of 200±5.0 mg with thickness of 2.24±0.2 mm.

Table 17 : Post compression Parameters of batch F1 to F12

Batch	Hardness (kg)	Disintegrating time (sec)	Wetting time (sec)	Water absorption ratio	Friability (%)	Average Weight
F1	2.0-3.0	56	42	19.45	0.49	199
F2	2.0-3.0	45	33	24.89	1.36	199
F3	2.5-3.5	27	45	23.09	0.19	200
F4	2.5-3.5	36	43	25.56	0.16	199
F5	2.5-3.5	25	54	20.19	0.14	196
F6	2.5-3.5	21	55	23.34	0.18	196
F7	2.5-3.5	30	45	24.35	0.15	200
F8	2.5-3.5	20	41	24.45	1.68	200
F9	2.5-3.5	16	46	25.14	0.21	201

F10	2.5-3.5	25	39	24.98	0.17	200
F11	2.5-3.5	18	44	25.43	0.35	199
F12	2.5-3.5	15	36	27.08	0.27	202

In vitro dissolution study:

Table 18 : Dissolution study of Formulation Batch F1 to F6.

Time (min)	% Drug Release in 900ml pH 6.8 Phosphate buffer 50 RPM, 37°C ± 0.1°C, USP Type II (Paddle)					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
2	1.91	0.94	4.31	4.04	6.41	14.82
4	3.02	4.47	17.26	8.59	12.27	51.35
6	4.62	5.42	34.96	12.98	29.31	69.19
8	6.31	5.44	44.79	17.99	32.59	81.57
10	7.95	7.06	54.08	32.59	38.96	88.13
15	10.90	9.81	66.64	39.14	49.89	98.32
20	14.54	11.58	79.21	47.70	56.08	101.78
25	16.42	13	86.49	56.26	57.72	
30	24.94	14.62	91.95	62.82	63.91	
40	28.95	30.59	96.32	72.83	74.65	
45	33.68	33.32	96.69	77.38	79.18	
60	38.60	40.24	100.87	90.86	101.97	

Figure 11 : Dissolution profiles of Dexibuprofen ODTs of batch (F1 – F3)

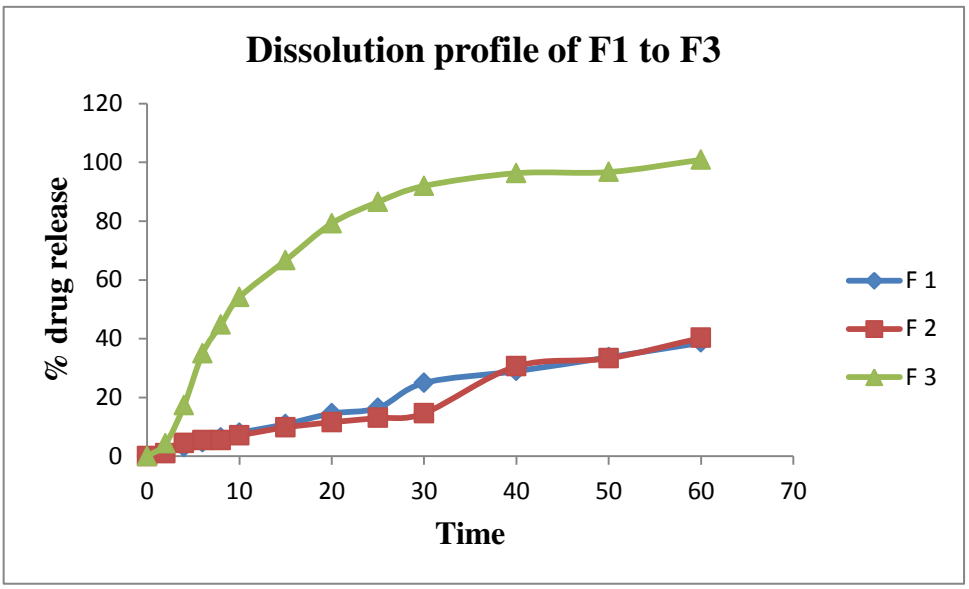


Figure 12 : First–order release profiles of Dexibuprofen ODTs of batch (F1 – F3)

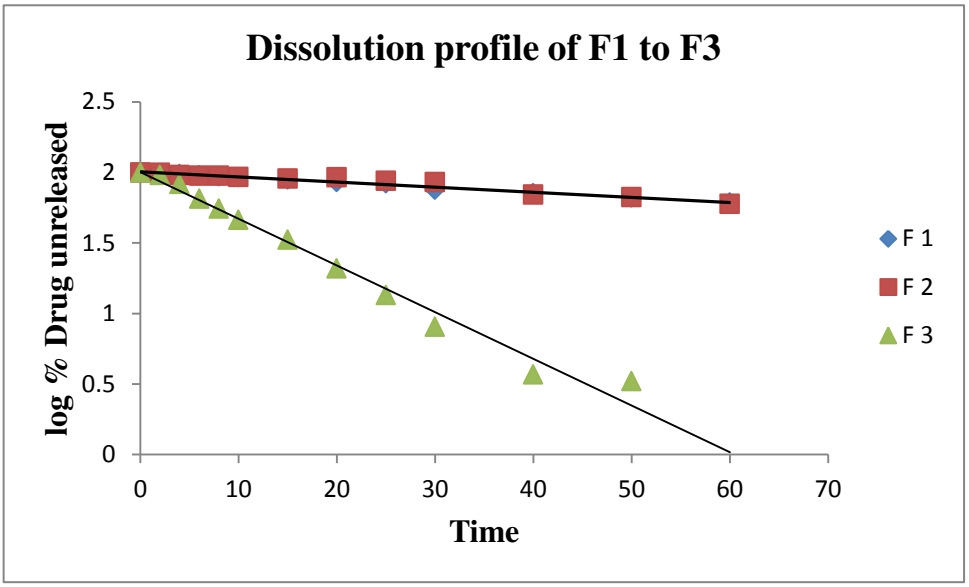


Figure 13 : Dissolution profiles of Dexibuprofen ODTs of batch (F4 – F6)

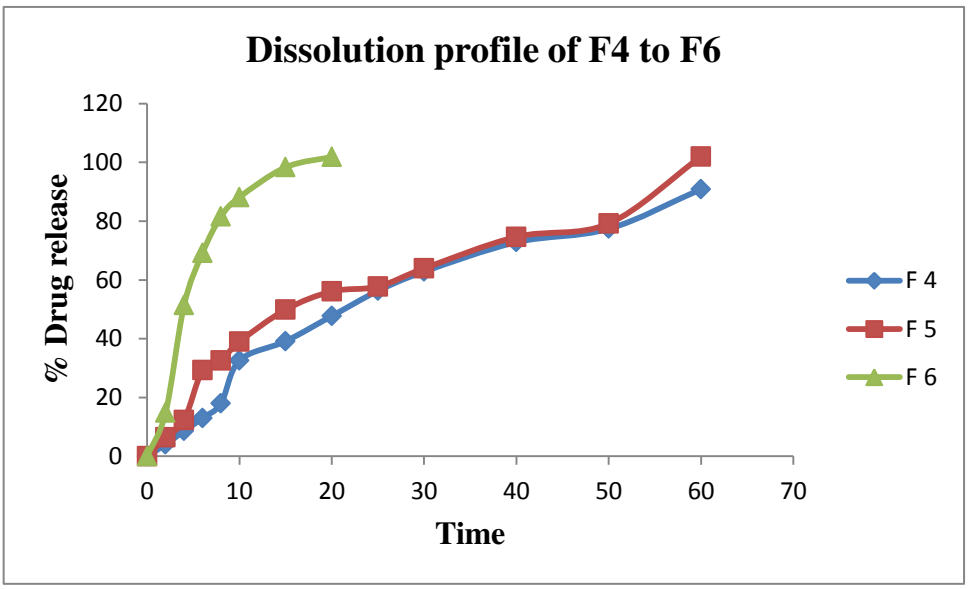


Figure 14: First–order release profiles of Dexibuprofen ODTs of batch (F4 – F6)

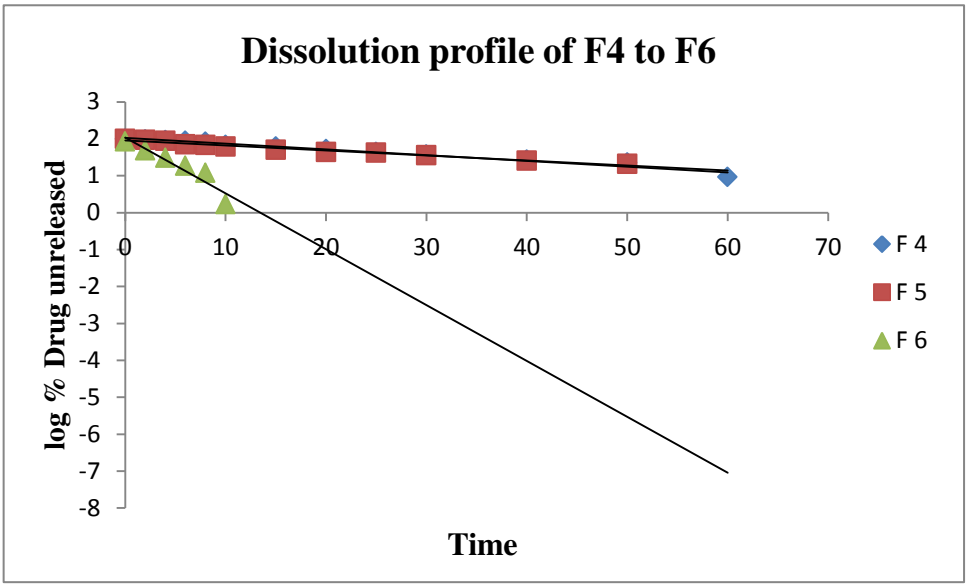


Table 19 : Dissolution study of Formulation Batch F7 to F12

Time (min)	% Drug Release in 900ml pH 6.8 Phosphate buffer 50 RPM, 37°C ± 0.1°C, USP Type II (Paddle)					
	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
2	1.14	33.32	29.13	3.71	38.6	69.92
4	2.74	58.26	62.27	10.48	66.2	90.68
6	7.33	85.03	81.75	27.13	87.58	98.86
8	12.47	91.77	90.68	30.22	96.69	102.88
10	16.09	94.14	97.05	39.15	102.88	
15	35.14	97.78	102.18	51.89		
20	48.07	98.14		61.54		
25	54.08	98.44		72.1		

30	65.53	98.86		76.66		
40	81.21	102.05		90.13		
45	93.95			92.86		
60	93.95			94.5		

Figure 15 : Dissolution profiles of Dexibuprofen ODTs of batch (F7 – F9)

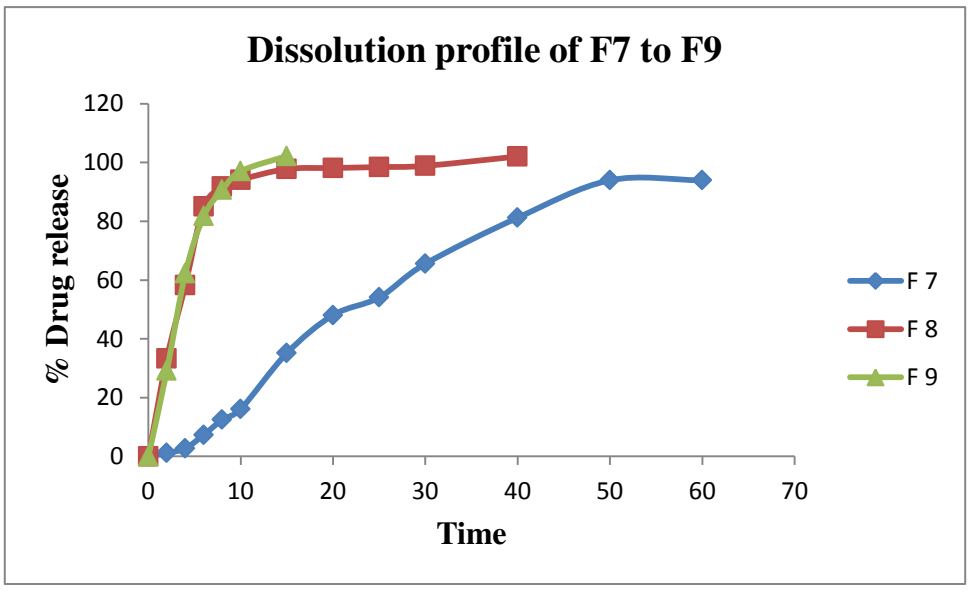


Figure 16: First–order release profiles of Dexibuprofen ODTs of batch (F7 – F9)

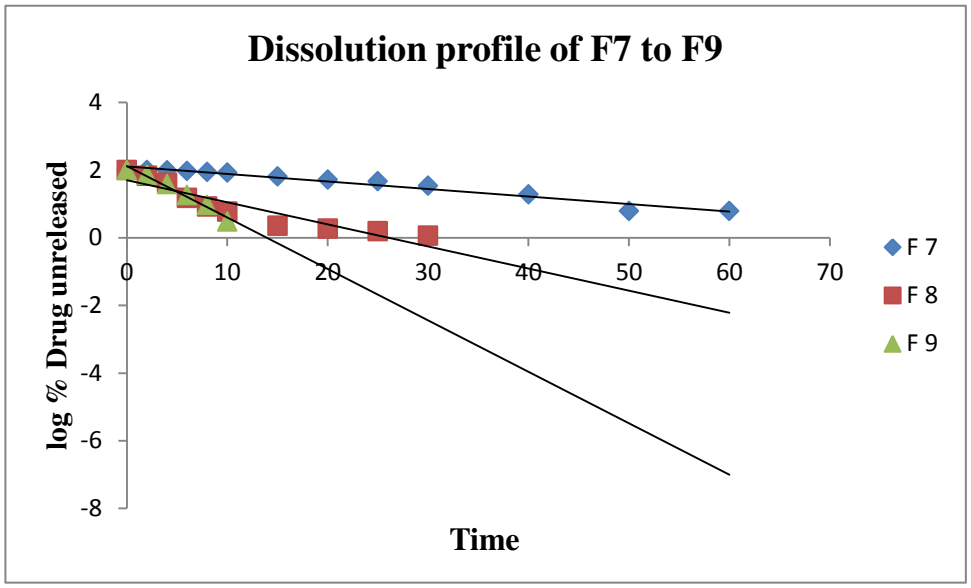


Figure 17 : Dissolution profiles of Dexibuprofen ODTs of batch(F10–F12)

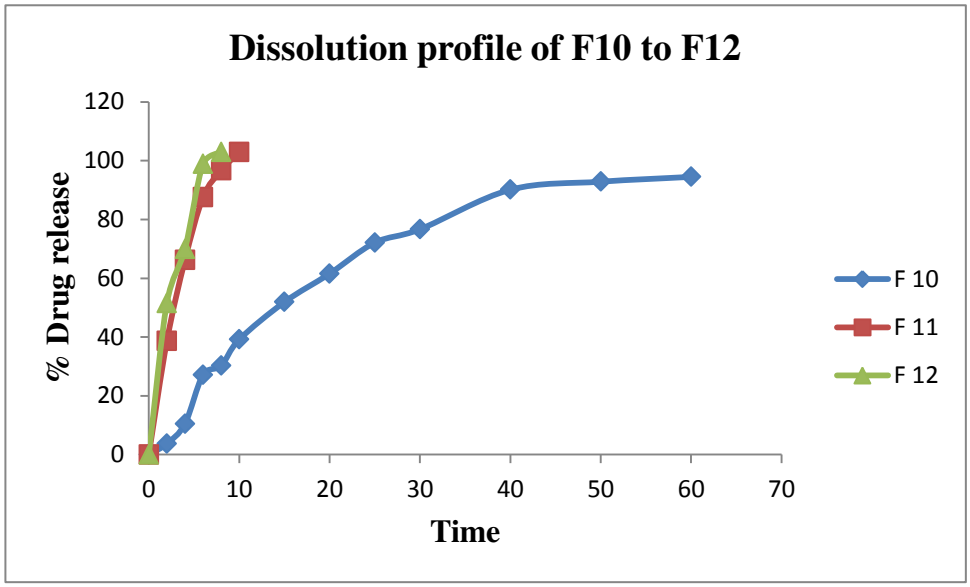
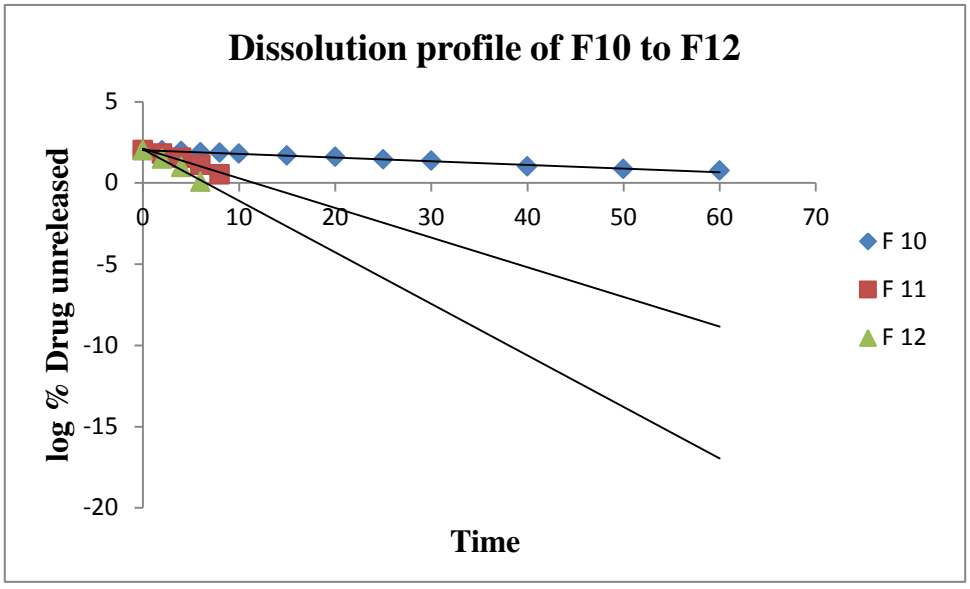


Figure 18: First–order release profiles of Dexibuprofen ODTs of batch(F10–F12)



The tablets of various formulations were subjected to various evaluation tests, such as thickness, weight variation, friability, hardness, and drug release by dissolution studies

according to the procedure specified in the I.P. The results of the tests were tabulated and found to be within the Pharmacopoeial limits. This study indicated that all the prepared formulations were good.

The disintegration times of Dexibuprofen ODTs containing Sodium starch glycollate as superdisintegrant were low when compared to those of other formulations. The increasing order of effectiveness of superdisintegrants with respective to the disintegration time in Dexibuprofen ODT's was found to be

Sodium starch glycollate > croscarmellose sodium > crospovidone

Again in formulations containing Sodium starch glycollate i.e. F3, F6, F9, F12, formulation F12 of 8% concentration of superdisintegrant show low disintegration time.

Finally, the dissolution test showed that the dissolution rates of Dexibuprofen ODT's containing sodium starch glycollate as superdisintegrant were high than other formulations, Among the formulations containing Sodium starch glycollate, i.e. F3, F6, F9, F12, formulation F12 of 8% concentration of superdisintegrant shows high dissolution rate. So, by considering all results of pre-compression and post-compression parameters formulation F12 is considered as optimized formulation.

5.3 STABILITY STUDIES OF OPTIMIZED FORMULATION

Table 20 : Comparison profile of stability batch, initial and 1 month

Parameter	Condition 40° C / 75% RH	
	Initial	1 months
Hardness	2.5-3.5	2.5-3.5
Friability	0.27	0.29
Disintegration time	15	16
Wetting time	36	42

Table 21 : Dissolution profile of stability batch, initial and 1 month.

Time (min)	% drug release	
	Initial	1 months
0	0	0
2	69.92	70.2
4	90.68	90.1
6	98.86	99.4
8	102.2	100.6

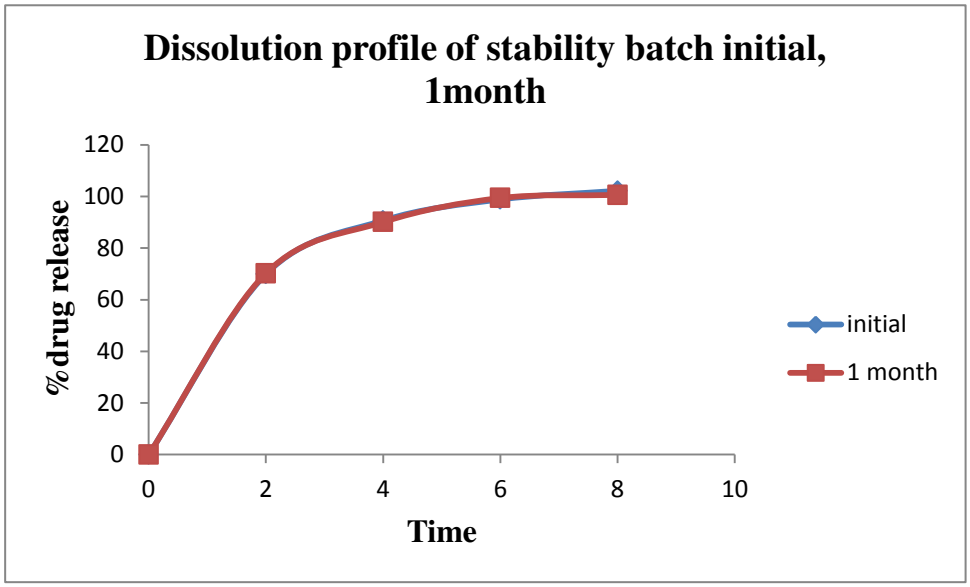


Figure 19 : Dissolution profile of Stability batch of initial and 1 months for optimized formulation

Table 22 : Drug release kinetics of Dexibuprofen ODT Formulations F1 - F12

FORMULA	Zero order		First order	
	K_0	r^2	K_1	r^2
F1	0.689	0.983	0.007	0.992
F2	0.656	0.907	0.007	0.944
F3	2.326	0.534	0.076	0.98
F4	1.753	0.895	0.035	0.971
F5	1.904	0.782	0.030	0.973
F6	6.739	0.635	0.348	0.895
F7	1.857	0.952	0.051	0.959
F8	3.885	0.620	0.15	0.864
F9	9.048	0.654	0.348	0.974
F10	2.073	0.766	0.051	0.989
F11	12.13	0.863	0.419	0.957
F12	14.99	0.866	0.730	0.978

From the results of in-vitro drug release profile it was evident that kinetics of drug release was 1st order for all prepared ODT's as the plot between log% drug remained Vs time showed good linearity. The coefficient of regression (r^2) values closer to1.

6. CONCLUSION

The present work was aimed to develop a stable, safe and convenient oro-dispersible tablets of Dexibuprofen for rapid therapeutic action and to avoid first pass metabolism.

Dexibuprofen is a BCS class II drug, So rapid disintegration of the tablet was desired for achieving quick onset of action. For this purpose, suitable super disintegrants were added and tablets were disintegrated within seconds.

Twelve formulations of fast dissolving tablets of Dexibuprofen were successfully prepared using sodium starch glycollate, croscarmellose and crospovidone by direct compression method. We have manufactured ODTs with quality and product consistent by a production friendly direct compression technique which avoids costly technology, equipment and lengthy manufacturing process.

The tablets were evaluated for parameters like thickness, hardness, friability, in- vitro disintegration time, wetting time, water absorption ratio, and in- vitro drug release studies.

Based on the results, formulation containing 8% Sodium starch glycollate (F12) was identified as ideal and better formulation among all formulations developed for Dexibuprofen tablets.

In vitro release of optimized formulation of Dexibuprofen fast dissolving tablets of F12 was found to be 98.86% drug release within 6 min.

The optimized formulation was subject to stability studies for 1 month by storing them at 40C/75%RH. Results of physical appearance, hardness, friability, disintegration test, and % drug release have shown that there was no significant change at storage condition. They were within the limits as per stability protocol given in ICH guide lines in formulations.

Thus, Dexibuprofen oro-dispersible tablets were successfully developed.

7. SUMMARY

Dexibuprofen is an non-steroidal anti-inflammatory drug (NSAID) , a propionic acid derivative with analgesic and antipyretic properties. Dexibuprofen inhibits cyclooxygenases and activates peroxisome proliferators-activated receptors; both of these actions result in reduced inflammation.

Dexibuprofen is an NSAID that is advocated for the treatment to relieve pain and inflammation associated with osteoarthritis, dysmenorrhea. Apart from pain it is also used in treatment of pain associated with toothache and other painful problems of the muscles and bones. Dexibuprofen is rapidly eliminated from the body due to hepatic metabolism. Thus by formulating it as ODT its degradation by liver can be bypassed and thus, its bioavailability can be increased

The present study is an attempt to develop and formulate fast dissolving tablets of Dexibuprofen with superdisintegrants which disintegrates in matter of seconds in the oral cavity, thereby reducing the time of onset of pharmacological action and to prevent the first pass metabolism of Dexibuprofen.

In this system direct compression was used, Microcrystalline cellulose (MCC) is used as a diluent, sodium starch glycollate (SSG), croscarmellose sodium and crospovidone(CP) were used as superdisintegrants, aerosil are used as flow promoter, magnesium stearate was used as lubricant, aspartame as sweetener.

The drug- polymer compatibility was confirmed by FTIR studies. The results obtained by FTIR studies revealed that there was no chemical interaction between the pure drug and excipients. Direct compression method was employed to formulate the tablets, because of its cost effectiveness and due to reduced number of manufacturing steps.

The pre-compression parameters like bulk density, tapped density, Carr's 'index and angle of repose were determined. The final formulation showed acceptable flow properties. The post-compression parameters like the thickness, hardness, friability and in vitro disintegration time, wetting time, water absorption ratio and in vitro drug release were carried out and the values were found to be within IP limits.

The final optimized formulation of Dexibuprofen tablets containing 8% Sodium starch glycollate (F12) revealed that formulated rapid dissolving tablets of Dexibuprofen were effective and better to meet patient compliance.

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